

Chlorinated Hydrocarbon Insecticides

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15.1 CLASSIFICATION OF CHLORINATED HYDROCARBON INSECTICIDES

All chlorinated hydrocarbon insecticides are aryl, carbocyclic, or heterocyclic compounds of molecular weights ranging from about 291 to 545. Their cyclic structure and their greater molecular weight set them apart chemically from the chlorinated hydrocarbons used as solvents and fumigants (molecular weight < 236), which are described in Chapter 14. In a biological context the chlorinated hydrocarbon insecticides also differ from the chlorinated hydrocarbon solvents in that the former are generally stimulants of the nervous system while the latter are depressants. However, this distinction is not absolute: the γ -isomer of benzene hexachloride (γ -BHC; lindane) is a stimulant, but two other isomers have an opposite effect.

The chlorinated hydrocarbon insecticides may be divided into five groups: DDT and its analogs, BHC, cyclodienes and similar compounds, toxaphene and related chemicals, and the caged structures mirex and chlordcone. There is a greater tendency of insects to develop overlapping resistance to insecticides within each group than between groups, the latter probably reflecting differences in modes of action. However, overlapping of resistance between groups does occur.

In spite of some similarity of chemical structure and pharmacological effect, the individual insecticides within each group differ widely in toxicity and in their capacity for storage. Furthermore, toxicity and storage do not always vary in a parallel way. Methoxychlor is much less toxic and much less stored than DDT, whereas endrin, which is more toxic than dieldrin, is stored far less. Thus, each compound must be judged separately.

Although the organochlorine insecticides were widely used in agriculture and malarial control programs from the 1940s to 1960s with dramatic beneficial effects, they have come into disfavor because of their persistence in the environment, wildlife, and humans. The relatively low cost of these insecticides and unavailability of complete substitutes for some uses, how-

ever, ensure their continued use in many countries for some years to come.

The structures of the different chlorinated hydrocarbon insecticides are shown in the appropriate sections: DDT and analogs in Section 15.3, BHC in Section 15.4, cyclodienes in Section 15.5, toxaphene in Section 15.6, and mirex and chlordcone in Section 15.7.

15.2 TOXICOLOGY OVERVIEW

15.2.1 SYMPTOMATOLOGY

In general, the signs of poisoning produced by different chlorinated hydrocarbon insecticides are similar, that is, expressions of neuronal hyperactivity. However, there are certain differences between the effects of DDT and its analogs, on the one hand, and all other chlorinated hydrocarbon insecticides on the other. Not only is tremor characteristic of poisoning by DDT, but also the onset of poisoning by it occurs with easily detectable mild effects that progress gradually, but continuously, to the point of convulsions. In contrast, lindane, aldrin, dieldrin, endrin, toxaphene, and several related compounds frequently produce illness in which a convulsion is the first sign of injury. This is true not only in experimental animals but also in people, who sometimes report that they experienced no prodromal symptoms of any kind prior to the initial fit. As described under Effects on the Nervous System in Section 15.3.1.2, with rats the incoordination associated with tremor induced by DDT may be demonstrated by measuring how long they can stay afloat in cool water. Whereas DDT causes marked reduction in swimming time at dose levels that cause no other clinical effect, dieldrin and some other pesticides interfere with swimming only at dosages that depress food intake and reduce weight gain so that it is reasonable to assume that the animals are weak. Thus it is probable that the incoordination observed in animals and people poisoned by these insecticides, other than DDT and its analogs, is different from

the tremor caused by DDT and should be referred to as ataxia or some other term.

The degree of stimulation of the nervous system appears to be related directly to the concentration of these insecticides in nerve tissue at the time. Usually the effect is rapidly reversible in animals after either single or multiple doses. Recovery occurs when the concentration of the chlorinated hydrocarbon insecticide in the nervous system falls below a critical level. It should be noted that this does not necessarily imply a loss of the chemical from the body but rather a redistribution to other tissues, such as adipose tissue, and has been studied particularly in connection with dieldrin (see Section 15.5.4.2).

15.2.2 ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

15.2.2.1 Routes of Absorption

All chlorinated hydrocarbon insecticides can be absorbed through the skin as well as by the respiratory and oral routes. The importance of dermal absorption varies greatly for the different compounds. This is partly because some of them, such as methoxychlor, have such a low toxicity that a small amount absorbed by any route is of no importance; more importantly, the efficiency of dermal absorption varies for the different insecticides. For example, DDT is poorly absorbed by the skin from solutions, and the absorption of solid material is so poor that it is difficult or impossible to measure either the uptake of DDT or its effect. In contrast, even solid dieldrin, if very finely ground, is absorbed so effectively through the skin that it is about half as toxic when applied dermally as when administered by mouth. The dermal penetration of these insecticides involves not only partition coefficients but also binding to various dermal, epidermal, and serum sites. This leads to complications in interpreting experimental findings from a kinetic viewpoint (Shah *et al.*, 1981).

Because of their relatively low vapor pressure, chlorinated hydrocarbon insecticides seldom reach levels in the air above those permitted. Of course, they may be absorbed from the lung if they reach the respiratory epithelium in the form of solid or liquid aerosols of appropriate particle size.

The intestinal absorption of lipophilic substances such as these insecticides will be influenced by fiber and fat constituents of the diet as well as by the total food intake. The absorption of dieldrin, for instance, is enhanced by starvation (Heath and Vandekar, 1964).

15.2.2.2 Distribution, Metabolism, and Excretion

Chlorinated hydrocarbon insecticides have become infamous because of their tendency to accumulate in humans, animals, birds, and the general environment. After single or repeated doses, most of these chemicals eventually reach their highest concentrations in adipose tissue with somewhat lower levels in other tissues with high contents of neutral lipids, such as adre-

nals. Although storage in adipose tissue can be partly explained by the lipophilicity of these insecticides, other factors such as structural elements of the chemical and competition between binding sites in lean and adipose tissue are of great importance (Bickel, 1984). Another, perhaps even more important factor is the rate of metabolism and excretion of the parent chemical and any metabolites. For instance, DDT and its primary metabolite DDE are stored in adipose tissue of humans, whereas the closely related insecticide methoxychlor, which is metabolized much more rapidly, occurs in fat only at very low levels. Indeed, this difference has led to the increasing use of methoxychlor as an insecticide with the decline in the popularity of DDT. The isomers of BHC are stored to very different degrees in a pattern that does not correspond to their solubility in body fat (see Section 15.4.1.2) and is probably due to some extent to differential metabolism. Dieldrin is stored avidly, whereas its isomer endrin is stored so little that it has been detected in patients only after acute exposure and not even in people engaged in its manufacture (see Section 15.5.3). Again, this is due to differential metabolism; the unhindered *anti*-C-12 hydrogen in endrin makes this position far more susceptible to attack than any other position in either isomer (Bedford and Hutson, 1976). Metabolites of dieldrin are thus excreted at a much lower rate in bile and feces than are those from an equal dose of endrin (Cole *et al.*, 1970). Of course, in itself, storage of chemicals in adipose tissue can be viewed as a detoxification mechanism.

The specific metabolic transformations undergone by chlorinated hydrocarbon insecticides are covered in the appropriate sections. General principles of these metabolic routes are discussed in Chapter 3. In common with other lipophilic xenobiotics, chlorinated hydrocarbon insecticides can be metabolized by the microsomal cytochrome P-450 system to hydroxyl derivatives, perhaps with dehydrochlorination as observed for lindane, or by conversion to stable epoxides as in the case of the formation of dieldrin from endrin. The *O*-dealkylation of methoxychlor probably also involves a cytochrome P-450-mediated hydroxylation step. Other routes of metabolism involve conjugation with glutathione to give eventually mercapturates which are usually excreted in the urine (see Section 15.4.1 for lindane), or the production of glucuronides, as in the case of the alcohol formed by reduction of chlordecone (see Section 15.7.2).

Parent insecticides are usually excreted either in the bile or possibly through the intestinal wall. Both routes may be manifested ultimately as fecal excretion. Metabolites of the chlorinated hydrocarbon insecticides can also be excreted in the urine if they are of relatively high polarity. This may have involved resorption of conjugates from the intestinal tract and transport to the liver and kidney (enterohepatic circulation) followed by further metabolic transformations. Such would be the case for glutathione conjugates excreted in bile, some of which may be reabsorbed and converted to the mercapturates for urinary excretion.

An important consideration when discussing the excretion of chlorinated hydrocarbon insecticides is their presence

milk (Jensen, 1983). The lipid content of milk (3–5%) and high blood flow to breast tissue can lead to considerable concentration of these chemicals compared to that in tissues. Thus, contamination of both cow's milk and human milk is not just a form of excretion but a unique one that could also lead to toxic effects in the recipient. Infants in countries with a large use of insecticides could be at particular risk, especially since breast feeding is recommended by the World Health Organization and other health agencies. Levels of these chemicals in human milk can be 10 times those in cow's milk. Measurement of chlorinated hydrocarbon insecticides in human milk is a convenient method for determining exposure of populations to these compounds, although it is prone to variability due to the effects of age, smoking, diet, and other factors (Jensen, 1983).

The excretion of DDT, DDE, and dieldrin in association with hair has been reported (Matthews *et al.*, 1976), probably representing their presence in hair or skin oils.

15.2.2.3 Factors Influencing Storage and Toxicity

Although the interaction of pesticides among themselves or with other chemicals is outlined in Chapter 2, it is pertinent here to discuss the interaction between chlorinated hydrocarbon insecticides. The ways in which these compounds influence the metabolism of themselves or of others of the same group is complex and still poorly understood. The results are essentially opposite in some species compared to others.

In dogs, when dieldrin and DDT are administered together, the storage of dieldrin is decreased but that of DDT is *increased* compared to the storage when each insecticide is given separately (Deichmann *et al.*, 1971a). If both aldrin and DDT are fed simultaneously to dogs, the storage of both compounds is increased such that the storage of aldrin is about the same, and the storage of DDT, and especially DDE, is somewhat greater than when each compound is given alone but at twice the dietary concentration (Deichmann *et al.*, 1969).

In the trout the situation is similar to that in dogs (Mayer *et al.*, 1970; Macek *et al.*, 1970), and in trout methoxychlor behaves like DDT when combined with other compounds (Mayer *et al.*, 1970).

In Japanese quail, the storage of DDE is increased in the presence of dieldrin but the latter remains essentially unchanged (Ludke, 1974).

In rats, when the compounds are combined, the storage of dieldrin is markedly decreased while the storage of DDT is uninfluenced (Street, 1964; Street and Chadwick, 1967; Street and Blau, 1966; Pearl and Kupfer, 1972; Street *et al.*, 1966a,b). The actions of methoxychlor and hexachlorobenzene (Avrahami and Gernert, 1972) are similar to that of DDT in reducing dieldrin storage. Hexachlorobenzene (*not* BHC) will also reduce storage of aldrin but increase the storage of DDT and mirex (Clark *et al.*, 1981). At the same time, polar urinary metabolites of the insecticides are increased from aldrin and mirex but remain unchanged from DDT. Storage of heptachlor in rats is depressed by DDT (Street *et al.*, 1966b) and excretion

of [¹⁴C]dieldrin administered ip is stimulated (Pearl and Kupfer, 1972).

In guinea pigs, when DDT and dieldrin are fed together, the storage of dieldrin is little affected but that of DDT is decreased (Wagstaff and Street, 1971b).

Undoubtedly, the interaction of compounds of this type in different species depends in part on their ability to induce the microsomal drug-metabolizing enzymes in those species. However, relationships between induction, storage, and excretion of metabolites are rarely simple and there are few studies of the induction of the metabolism of one pesticide by another. Lindane and DDT have been found to be only moderately active inducers in guinea pigs although their storage is low, whereas dieldrin was a strong inducer, yet its storage is much higher than that of the other two insecticides (Wagstaff and Street, 1971b). In mice, treatment for 5 months with DDE decreased the urinary excretion of [¹⁴C]DDE and increased hepatic levels (Gold and Brunk, 1986). However, there was no effect on the levels of the only metabolite detected, 1,1-dichloro - 2 - (4-chlorophenyl) - 2 - (3-hydroxy-4-chlorophenyl) ethane. It is very difficult to interpret experimental findings of this type in the context of human exposures both of the general population and of heavily exposed workers. Dose levels and routes of administration in experimental animals are usually much different from those experienced by humans. Thus there are few studies of the effects of these pesticides on their own metabolism or that of other insecticides in humans. One possible example is the finding that current and former endrin workers stored significantly lower levels of *p,p'*-DDE; in fact, the levels were below detectable limits (Jager, 1970).

Other xenobiotics and drugs will undoubtedly affect the storage, distribution, and metabolism of chlorinated hydrocarbon insecticides as described above for hexachlorobenzene. Recent progress in our understanding of the induction of the drug-metabolizing systems (e.g., cytochrome P-450 and glutathione transferase isoenzymes) in both animals and humans and the influence of age, sex, and genetics, however, should make interactions easier to predict.

The combined effect of chlorinated hydrocarbon insecticides and anticholinesterase insecticides is one form of interaction that has received special attention even though there is no evidence that it has ever been of any clinical importance. Pretreatment of experimental animals with various chlorinated insecticides (including aldrin, dieldrin, chlordane, and DDT) has afforded some protection against single doses of some anticholinesterases (Triolo and Coon, 1966a,b; Williams and Casterline, 1970; Deichmann and Keplinger, 1970; Bass *et al.*, 1972). In other instances, the toxicity of an organophosphorus insecticide is increased by pretreatment with chlorinated hydrocarbon insecticides. For example, the toxicity of fenitrothion in rats is increased by heptachlor (Mestitzová *et al.*, 1970a,b, 1971). In one case, protection by aldrin against para-thion appeared after 16 hr, reached a maximum in 4 days, and lasted at least 12 days. A dose of 1 mg/kg provided significant protection (Triolo and Coon, 1966a,b). Most of these enhancing or protective effects of chlorinated hydrocarbon

insecticides are probably the consequence of induction of particular routes of metabolism and should now be mostly predictable. Piperonyl butoxide, an inhibitor of cytochrome P-450, will block the protective action of chlorinated insecticides on 6-chloro-3-xylyl methylcarbamate (Williams and Casterline, 1970). Chlorinated hydrocarbon insecticides appear to have an affinity for a hydrophobic site of cholinesterase although they do not inhibit the active site of the enzyme (Mayer and Himel, 1972); whether this interferes with the approach of the substrate to the active site is not known.

Mobilization of fat in adipose tissue due to starvation or other reasons can release into the circulation stored chlorinated hydrocarbon insecticides, sometimes with marked effects.

15.2.3 MODES OF ACTION AND CAUSE OF DEATH

15.2.3.1 Effects on the Central Nervous System

Mode of Action As discussed elsewhere (Section 4.1.2.3), there is considerable evidence to suggest that the chlorinated hydrocarbon insecticides act by altering the electrophysiological and associated enzymatic properties of nerve cell membranes, causing a change in the kinetics of Na^+ and K^+ ion flow through the membrane. Disturbances of calcium transport or Ca^{2+} -ATPase activity may also be involved, as well as phosphokinase activities (Matsumura and Patil, 1969; End *et al.*, 1981; Joy, 1982a; Shankland, 1982; Tilson and Mactutus, 1982; Woolley *et al.*, 1985; Ishikawa *et al.*, 1989). Other cell membranes may also be affected by related mechanisms. Dieldrin at a concentration of 10 μM affects liver cell membranes in a way very similar to that of the insect nervous system *in vivo* (Wang and Matsumura, 1969). DDT and some of its analogs (but not others) have been shown to inhibit Ca^{2+} -ATPase from human term placentas (Treinen and Kulkarni, 1986). Most studies have been conducted with DDT (Section 15.3.1.2) and chlordcone and other cyclodienes (Section 15.7.2.2). Full explanations for the differences in the *in vivo* neurotoxic effects of these two groups of chlorinated hydrocarbon insecticides are still not completely apparent, including the peripheral versus central nervous system (CNS) actions. DDT and its analogs appear to act particularly at the nerve axon by prolonging opening of the ion gates of the sodium channel (Ishikawa *et al.*, 1989), whereas cyclodienes, mirex, and lindane seem to act at presynaptic terminals. Lindane, toxaphene, and cyclodienes have been shown to inhibit *t*-butylbicycophosphorothionate binding to brain specific sites, indicating action at the γ -aminobutyric acid (GABA)-regulated chloride channel (Casida and Lawrence, 1985; Cole and Casida, 1986). DDT, mirex, and chlordcone had no effect. Cyclodienes and lindane also inhibit GABA-induced ^{36}Cl influx into rat brain membrane microsacs (Abalis *et al.*, 1986).

Whatever the exact mechanisms, nonconvulsant doses of chlorinated hydrocarbon insecticides increase the susceptibility of animals to convulsions precipitated by many other poisons or by electroshock. One study of this relationship concluded

that the convulsant effects of dieldrin may be mediated by effects on the hippocampus and other limbic structures (Swanson and Woolley, 1978). Fonseca *et al.* (1986) have demonstrated that *p,p'*-DDT and lindane decrease the number of muscarinic receptor sites in selective regions of rat brain.

A toxic dosage of dieldrin (50 mg/kg) led to a decrease in norepinephrine in the brain of rats 5 hr after ingestion but no change in dopamine or serotonin. When rats were maintained on a dietary level of 80 ppm (about 2.4 mg/kg/day) that they tolerated well for more than 10 weeks, norepinephrine and serotonin (but not dopamine) were depleted in certain parts of the brain soon after feeding but later returned to normal values (Wagner and Greene, 1974). A decrease in brain stem norepinephrine and acetylcholine and an increase in serotonin have been observed in rats following toxic doses of several cyclodiene insecticides (Hrdina *et al.*, 1974). Similar changes were seen with DDT (Hrdina *et al.*, 1973). It is clear that changes in the biogenic amines parallel the toxicity of chlorinated hydrocarbon insecticides, including the phenomenon of initial illness followed by clinical recovery. Whether these changes in the biogenic amines are a cause or a consequence is not clear. What is certain is that a variety of stimuli, including electrical stimuli and some insecticides, can change the production of biogenic amines in the brain (Campos and Jurupe, 1970).

The relative acute toxicities of the chlorinated hydrocarbon insecticides in animals and humans have been listed by Joy (1982a). The cyclodienes endrin, dieldrin, and isobenzan appear to be among the most toxic to humans and perhaps >10-fold more acutely toxic than DDT, which is the most potent agent in the dichlorodiphenylethane group.

Origin of Fever Fever may be a specific result of poisoning of the temperature control center in the brain. The effect may be more common than has been recognized. What has been recognized in a few human cases is high fever of sometimes late but sudden onset, frequently followed promptly by death. This kind of fever has been observed in poisoning by BHC, dieldrin, and endrin.

Fortunately, high fever of central origin is rare, but because it is such a grave sign, it is essential to distinguish it from other kinds of fever that may be the result of poisoning. Fever may accompany convulsions in humans or larger animals simply because it may be impossible to dissipate heat as rapidly as it is generated by the violent activity, which certainly is muscular and may be metabolic also. Fever of this origin has no special prognostic significance beyond that of the convulsions that give rise to it.

Regardless of the exact cause, a moderate increase in body temperature during the early course of illness carries no serious implications (Osuntokun, 1964). However, unless fever subsides promptly after convulsions are controlled, some other basis for it must be sought.

Fever may also be a response to chemical pneumonitis following aspiration of solvents or other chemical irritants; of course, fever of this origin may occur after a formulation of

any chlorinated hydrocarbon insecticide has been aspirated. It may depend in part on secondary infection. Usually it is delayed about 12 hr or more, and in relatively mild cases it may not appear until the patient has recovered from neurological manifestations.

EEG It is clear that the electroencephalogram (EEG) is a good index of the convulsive action of chlorinated hydrocarbon insecticides (Joy, 1982a). The sequence of EEG changes following a single convulsive dose of DDT and dieldrin to cats has been reported (Joy, 1973).

Pathology Chlorinated hydrocarbon insecticides produce little morphological change in the CNS of animals even when given in single or repeated doses sufficient to kill. The changes that do occur seem to reflect the agonal state but are not sufficient to account for death or assist in diagnosis, and they have been discussed by Joy (1982a).

15.2.3.2 Effects on the Liver

There is no doubt that DDT and a number of other chlorinated hydrocarbon insecticides cause marked changes in the livers of various rodents and that these changes progress to tumor formation in some species, especially the mouse. However, the relationship of these tumors arising in rodents to the potential induction of hepatocellular carcinoma in humans is still very obscure, as exemplified by DDT (Anderson, 1985), although the view that they are peculiar to rodents may not be completely justified, since for practical and financial reasons there have been few studies with other species.

Evidence for the carcinogenicity of chlorinated hydrocarbon insecticides has been reviewed by the International Agency for Research on Cancer (IARC) on a number of occasions during the last two decades. The IARC evaluation of these chemicals when administered by the oral route is shown in Table 15.1. Most of the insecticides produce tumors in mice, but results in rats are less conclusive. None of the chemicals have been completely negative in both rats and mice. Perhaps for this reason and the fact that their mechanism of action in liver has not yet been completely elucidated, the IARC seem reluctant to state categorically that they pose no carcinogenic risk to humans.

In connection with DDT, which has been studied the most in this group of chemicals, it has been concluded that the evidence for carcinogenicity in humans is inadequate (IARC, 1982, 1987). In mice the oral hepatocarcinogenicity has been demonstrated in several strains and shows a dose-response relationship. A dietary level of 2 ppm (about 0.3 mg DDT/kg/day) produces a significant increase of hepatomas in male but not female CF1 mice and not in either sex of BALB/c mice. Increased tumor incidence (particularly lung adenomas) has also been reported in some other organs of mice. There is now clear evidence, confirming the preliminary studies of Fitzhugh and Nelson (1947), that DDT can be hepatocarcinogenic to rats (Rossi *et al.*, 1977; Cabral *et al.*, 1982b). Results in hamsters,

Table 15.1

Summary of the Oral Hepatocarcinogenicity of Some Chlorinated Hydrocarbon Insecticides in Animals as Assessed by IARC Working Groups on the Evaluation of Carcinogenic Risk of Chemicals to Humans (1974, 1979, 1982, 1983, 1987)^a

Chemical	Species	Evaluation
DDT	mouse	positive in both sexes and in various strains
	rat	positive
	hamster	negative
	dog	inconclusive
	monkey	inconclusive
	mouse	positive
methoxychlor	mouse	positive
	rat	inconclusive
chlorobenzilate	mouse	positive
	rat	inconclusive
dicofol	mouse	positive in males
	rat	inconclusive
BHC	rat	technical mixture, α isomer and γ isomer (lindane) positive; β isomer limited positive evidence
	mouse	inconclusive
chlordan	rat	positive
heptachlor	mouse	inconclusive
aldrin	rat	inconclusive
dieldrin	mouse	positive
	rat	negative or inconclusive
	dog	inconclusive
	monkey	inconclusive
endrin	mouse	inconclusive
	rat	negative or inconclusive
toxaphene	mouse	positive
	rat	negative
mirex	mouse	positive in two strains
	rat	positive
chlordecone	mouse	positive
	rat	positive

^a Evaluations for chlorobenzilate, methoxychlor, BHC, and toxaphene in rats may have to be revised; see Sections 15.3.4, 15.3.5, 15.4.1, and 15.6.1.

dogs, and monkeys appear to be still inconclusive, although hamsters do give liver tumors with *p,p'*-DDE, as do mice (Cabral, 1985). There appear to have been no new studies of the hepatocarcinogenicity of DDT in dogs and monkeys since those first reported (IARC, 1974). These studies, which were inconclusive, did continue for some time (monkeys up to 7.5 years), and though the numbers were small they were no less than those which had given positive results for other potential carcinogens.

Chlorinated hydrocarbon insecticides are, in general, negative in mutagenicity tests (Wildemauwe *et al.*, 1983). Whether their tumorigenicity in rodents is due to the promotion of spontaneous initiated events is not known. It is clear, however, that DDT, BHC, and the cyclodiene insecticides are efficient promoters of the actions of recognized potent hepatocarcinogens such as diethylnitrosamine and 2-acetylaminofluorene (Peraino *et al.*,

al., 1975; Williams and Numoto, 1984; Schulte-Hermann, 1985). The ability of these chemicals to cause tumors in the liver and promote those initiated by other carcinogens is probably tied up with the induction of microsomal and other enzyme systems. The following paragraphs are concerned with these matters.

Early Changes in the Rodent Liver Associated with Induction of Microsomal Enzymes The response of the rodent liver to DDT is entirely similar to its response to moderate dosages of BHC, chlordane, dieldrin, toxaphene (Lehman, 1951, 1952; Ortega *et al.*, 1956), and the important drug phenobarbital (Stevenson and Walker, 1969; Wright *et al.*, 1972; Thorpe and Walker, 1973). Similar early changes also were demonstrated in the livers of rats fed dimethrin, pyrethrins, and especially synergized pyrethrins (Kimbrough *et al.*, 1968) (see Chapter 13). Some of these lesions are also known to arise spontaneously (Popp *et al.*, 1985).

The earliest changes in some liver cells of rodents administered DDT involve so much increase in the smooth endoplasmic reticulum of individual cells that they enlarge, and the large granules that ordinarily are scattered throughout the cytoplasm are displaced to the periphery of the affected cell. Quite early, some of the endoplasmic reticulum forms whorls that may have fat droplets as their centers—this justifying the term “lipospheres” applied to them by Ortega *et al.* (1956, 1957). Others have referred to these inclusions as “hyaline oxyphil masses” (Lillie and Smith, 1944), “lamellar bodies” (Ito *et al.*, 1973), or “myelin whorls” (Hansell and Ecobichon, 1975). These changes are accompanied by some increase in fat droplets, not all of which become surrounded by endoplasmic reticulum. This cluster of changes (hypertrophy, margination, and lipospheres) is characteristic of the response of rodents to compounds that induce microsomal enzymes. The characteristic changes develop promptly. An increase in smooth endoplasmic reticulum and the appearance of lamellar structures have been seen as early as 4 and 7 days after dosing began (Wright *et al.*, 1972). When DDT was administered to rat dams by stomach tube for 3 days at the rate of 50 mg/kg/day, no significant induction of liver microsomal enzymes and no morphological changes in the hepatocytes of the pups were observed prior to their birth, even though residues were found in fetal tissues. The young of treated mothers did show increased smooth endoplasmic reticulum, lipid inclusions, and myelin whorls when they were 4 days old and thereafter, and no samples were collected from birth until day 4. Similar but somewhat lesser changes were produced on the same schedule by phenobarbital (75 mg/kg/day) (Hansell and Ecobichon, 1975).

The accumulation of lipid following a single large dose of dieldrin was reported to involve triglycerides only, with no increase in phospholipid or cholesterol. The increase in triglycerides was accompanied by increased incorporation of [¹⁴C]glucose into glyceride-glycerol but a decrease of its incorporation into fatty acids (Bhatia and Venkitasubramanian,

1972). Presumably, more triglyceride is formed in the presence of more glyceride-glycerol.

Certain changes other than the characteristic one have been reported but not confirmed. These include enlargement and morphological change of the mitochondria (Obuchowska and Pawlowska-Tochman, 1973; Watari, 1973), increased numbers of primary lysosomes, and atrophy of the Golgi body (Watari, 1973), none of which were found by Ortega (1966).

Although microsomal enzymes may be induced in other species, their livers do not seem to show the same morphological changes as viewed by light microscopy (Laug *et al.*, 1950; Lehman, 1951, 1952; Ortega *et al.*, 1956; Stevenson and Walker, 1969) or show them to a lesser degree as viewed by electron microscopy (Wright *et al.*, 1972).

The changes in liver cells that characterize induction of microsomal enzymes in rodents are distinct from the focal necrosis that may be produced with about the same ease in the livers of rodents or of other species by fatal or near-fatal dosages of chlorinated hydrocarbon insecticides. These necrotic lesions have been described by Smith and Stohlman (1944), Lillie *et al.* (1947), Nelson *et al.* (1944), Cameron and Burgess (1945), Deichmann *et al.* (1950), and Ortega *et al.* (1956). The necrosis does not appear to progress, since if high dosages are continued the animals die, whereas if dosing is stopped and the animals survive, the necrotic cells are removed by autolysis and phagocytic action. The lesions then heal, usually without scarring (Cameron and Burgess, 1945), although this can occur (Lillie and Smith, 1944; Lillie *et al.*, 1947). An interesting indication of the defensive or adaptive nature of the characteristic liver changes is the observation that they occur only in animals that remain healthy and not in animals that are frankly intoxicated by very high dosage levels (Ferrigan *et al.*, 1965). This does not mean that rats that have developed the changes may not later show signs of poisoning.

On the other hand, there is one aspect of the morphological change in the endoplasmic reticulum that may be even more critical than marked hypertrophy of the smooth variety in determining whether tumorigenesis will occur. Williams and Rabin (1971) reported that a range of established carcinogens promoted the degranulation of rat liver rough endoplasmic reticulum *in vitro*, whereas a range of noncarcinogens were without this effect. In a parallel way, carcinogens prevented smooth microsomal membranes from binding added ribosomes in the presence of estradiol. Wright *et al.* (1977) showed that results of biochemical tests for degranulation corresponded not only to the tumorigenicity of different compounds but also to differences in the susceptibility of different species and strains and of males and females of the same strain.

The Question of Reversibility and the Relation of Dosage to Induction of Microsomal Enzymes At least in their early stages, the changes in liver cells that characterize induction of microsomal enzymes in rodents are reversible (Fitzhugh and Nelson, 1947; Ortega *et al.*, 1956; Wright *et al.*, 1972). The reversibility does not depend on cell removal but simply on

reversion of the physiological and morphological condition of the cells to their original condition. Return of the liver to normal size also occurs if dosage is discontinued soon enough (Kunz *et al.*, 1966). On the other hand, normalization may be slow, especially when the inducer remains in the target tissue. Although the liver weight of rats returned to normal within 2 weeks after one or two doses of α -BHC at the rate of 200 mg/kg, the DNA content of the liver remained high, as did the proportion of the cells with tetraploid nuclei during a 7-week posttreatment period (Schulte-Hermann *et al.*, 1971). In rats fed photomirex (a degradation product of mirex) for 4 weeks (50 ppm), histological changes in the liver and thyroid could still be seen 48 weeks after return to normal diet (Chu *et al.*, 1981a,b). Consistent with these persistent changes was the finding of significant levels of photomirex remaining in the liver.

Of course, reversibility is incompatible with progression, but whether observed irreversibility will be associated with progression must be determined directly in each instance. In the following paragraphs, the question of progression is discussed only after consideration of the problem of irreversibility in general.

If dosing with chlorinated hydrocarbon insecticides or other inducers is continued long enough and at a sufficiently high level, the liver changes become irreversible, if for no other reason than that the remaining life span of the animals is too short to permit excretion of the inducing chemical or complete reversion of the liver cells to their original state. Just when this shift to irreversibility occurs remains unknown, but it seems very likely that dosages sufficient to produce irreversible morphological change also exceed the physiological adaptability of the liver. The important distinction between adaptation and injury as it relates to enzyme induction and liver morphology has been studied in relation to dieldrin (see Section 3.1.2.3). The matter has received some biochemical study, which suggested that hypoactive hypertrophic endoplasmic reticulum involves a qualitative change in the induced cytochrome P-450 (Stevens *et al.*, 1977).

Briefly, the evidence is strong that enlargement of the liver and of individual liver cells is adaptive at dosages where the increase in endoplasmic reticulum is accompanied by a parallel increase in activity of the associated enzymes and by no depression in the activity of other enzymes and that these liver changes are pathological at higher dosages where the activity of the drug-metabolizing enzymes fails to keep pace with the morphological changes or where the activities of these or other enzymes are depressed.

The relation of dosage to the induction of microsomal enzymes has been discussed previously (see Sections 2.3.8 and 7.4.3). The effects of DDT were explored by Kinoshita *et al.* (1966) and later studied more thoroughly by Hoffman *et al.* (1970). They found that, when DDT was fed to male weanling rats for only 14 days at dietary concentrations of 0.5–2048 ppm, concentrations of 0.5 and 2 ppm had no effect on the *O*-demethylation reaction used as a test, but concentrations of 4–750 ppm produced increases in the rate of metabolism propor-

tional to the log of dosage. Extrapolation of this portion of the dosage-response curve to the abscissa provided a calculated no-effect level of 3.27 ± 1.02 ppm equivalent to about 0.327 mg/kg/day. This is in reasonable agreement with other estimates of the threshold for induction of various enzymes in the rat, including some studies involving longer administration of DDT. These estimates, expressed as milligrams per kilogram per day, are approximately 0.05 (Kinoshita *et al.*, 1966; Street *et al.*, 1969), 0.5 (Schwabe and Wendling, 1967), and 0.125 (Gillett, 1968). The relationship may not be the same for different inducers in the same species or for the same inducer in different species or sexes. For example, DDT in the squirrel monkey promotes the metabolism of EPN and *p*-nitroanisole; the first requires a DDT dosage of 5.0 mg/kg/day, but the latter requires only 0.5 mg/kg/day (Cranmer *et al.*, 1972). *In vivo* administration of both chlordcone and mirex induces the V_{max} of *p*-nitroanisole metabolism by male rat microsomes and increases apparent K_m values, but with females this metabolism was reduced with either agent and the apparent K_m value was elevated by chlordcone but little affected by mirex (Ebel, 1984). Metabolism of DDT is promoted by DDT itself in the hamster (Gingell and Wallcave, 1974) but not in the mouse (Gingell and Wallcave, 1974) or in the squirrel monkey (Chadwick *et al.*, 1971b). However, most of the estimates for minimal effective dosage are of the same order of magnitude as 0.25 mg/kg/day, known to be effective in humans (Poland *et al.*, 1970), but all are more than 100 times greater than the highest dosage of people in the general population during the late 1960s (Duggan, 1968). In the study by Hoffman and his colleagues (1970), increase of the dietary level above 750 ppm produced no further increase in enzyme activity. Intake less than 128 ppm produced no increase in liver weight within the period of observation; increase was proportional to dosage within the range 128–512 ppm and was submaximal at intakes above 512 ppm.

The biochemical pattern of induction of mixed-function oxidase enzymes is similar for DDT and phenobarbital but distinctly different for 3-methylcholanthrene (Vainio, 1975). DDE, the major metabolite of DDT, was shown to induce mRNA for a cytochrome P-450 identical to that induced by phenobarbital but had a much more persistent effect (Morohashi *et al.*, 1984).

Late Changes in the Rodent Liver Associated with Induction of Microsomal Enzymes As indicated above, the earliest morphological changes caused by phenobarbital-type enzyme inducers in the rodent liver involve separate cells in the centrilobular area. If the dosage is sufficiently high and prolonged, nodules consisting entirely of hypertrophied cells may appear. At first, these microscopic nodules are distinguishable only by pattern; they have no bounding membrane and they do not compress or change in any other detectable way the smaller liver cells that surround them. Some nodules may become large enough to be seen without a microscope, and a few may exceed 1 cm in diameter. In these large nodules there is almost complete loss of lobular architecture. Nodules apparently were

first described by Fitzhugh and Nelson (1947), who felt they could be regarded as adenomas or as low-grade hepatic cell carcinomas. Just why this latter term was used is not clear because neither mitosis, tissue invasion, nor metastasis was observed. Although Ortega *et al.* (1956) reported small nodules in the livers of rats they had dosed and although they examined tissue loaned by Fitzhugh and Nelson's laboratory, they were entirely unimpressed by the lesions, referring to them as "focal incongruities."

The classification introduced by Thorpe and Walker (1973) and Walker *et al.* (1973) might have been expected to lead to better agreement or at least to a clearer definition of points of difference. As a result of their studies in mice, these investigators proposed that simple nodular growths of liver parenchymal cells be called type *a* lesions and that areas of papilliform and adenoid growth of tumor cells, sometimes accompanied by metastases to the lungs, be called type *b* lesions. It was concluded by Walker *et al.* (1973) on the basis of earlier studies of rats and dogs in their own laboratory and also on the basis of results of others that tumorigenic action of dieldrin had been demonstrated only in mice.

However, there still is no agreement regarding the carcinogenicity of the chlorinated hydrocarbon insecticides. The views of some pathologists remain diametrically opposite. This is true despite the finding of (a) pulmonary metastases of hepatic cells in mice that had received DDT (Tomatis *et al.*, 1972; Walker *et al.*, 1973), β -BHC, γ -BHC, dieldrin, or phenobarbital (Thorpe and Walker, 1973); or (b) progression of liver enlargement beginning 12 weeks after cessation of ingestion of α -BHC by mice for 24 or 36 weeks (Nagasaki *et al.*, 1974) or progressive increase in the size of liver nodules after DDT feeding was stopped (Tomatis *et al.*, 1974b; Tomatis and Turusov, 1975); or even (c) in BHC-exposed mice the time pattern of increase in liver weight (as reflected in body weight), which gained momentum only after a delay of 4 weeks but showed a further acceleration in week 13 in spite of decreased food consumption (Tomii *et al.*, 1972), which appears to establish without question that at least some of the liver changes produced by these compounds in rodents are malignant.

Of course, the reasons for disagreement are that tumors indistinguishable from those caused by DDT, other chlorinated hydrocarbon insecticides, and phenobarbital occasionally occur in control mice (Davis and Fitzhugh, 1962; Walker *et al.*, 1973) and rats (Fitzhugh and Nelson, 1947; Popp *et al.*, 1985) and, more especially, because these tumors differ from real cancers in their biochemistry and they are not malignant in the classical sense. Specifically, (a) they do not actively invade tissues, (b) their "metastases" usually do not grow even through large growths of liver cells in the lungs occasionally have been seen (Walker *et al.*, 1973), (c) any shortening of life span that occurs may be related to the toxicity of large dosages and not to tumors *per se*, and finally (d) mice receiving DDT at a rate of 5.5 mg/kg/day as a result of dietary intake show a decrease in the success of transplantation and a significant increase in survival following inoculation with an otherwise

uniformly transplantable and uniformly fatal ependymoma (Laws, 1971).

Although the displacement of liver cells to the lung occasionally seen after prolonged dosage with DDT usually is referred to as metastasis, it might better be called embolism because the lesion rarely progresses and, therefore, usually lacks the clinical significance of real metastasis. Because it usually does not grow, the lesion is usually hard to find. A number of investigators have failed to mention liver cells in the spleen, lymph nodes, or lungs, and some have stated specifically that they were not found (Nagasaki, 1973).

Perhaps the most illuminating studies of the liver changes caused by various chlorinated hydrocarbon insecticides are those in which 2,7-fluorinediamine, diazoaminobenzene, or some other classical carcinogen has been used as a positive control (Wright *et al.*, 1972; Walker *et al.*, 1973; Kuwabara and Takayama, 1974). In each case the lesion caused by the classical carcinogen was different from that caused by the insecticide in one or more of the following ways: (a) it did not involve induction of microsomal enzymes; (b) it started as hyperplastic nodules rather than as isolated cell changes; (c) bile duct proliferation or other lesions not found in controls or in insecticide-treated animals were present; (d) the final lesion was hepatocellular carcinoma, in contrast to the adenoma caused by DDT or BHC; and (e) α -fetoprotein was formed, which did not occur in connection with DDT or BHC. Other workers also have failed to find α -fetoprotein in mice treated with a chlorinated hydrocarbon insecticide (Hanada *et al.*, 1973).

It must be emphasized that the chlorinated hydrocarbon insecticides and phenobarbital do not produce in other animals, to the same extent, the early, visible changes in the endoplasmic reticulum that are so characteristic of some rodents and that may progress to tumor formation in them. The fact that these compounds do not lead to tumor formation in other animals might have been predicted by the fact that they do not cause in other animals the early changes, characterized by hypertrophy, margination, and lipospheres. Of course, it must also be said that the number of studies that have been conducted with nonrodent species are relatively few. In addition, chlorinated hydrocarbon insecticides may all be positive carcinogens in the mouse but not all seem to cause tumors in rats (see Table 15.1) despite considerable induction of the endoplasmic reticulum by other chemicals in the group. On the other hand, large increases in liver size after lindane treatment in CF1 mice but not B6C3F1 mice or Osborne-Mendel rats do seem to correlate with propensities for tumor formation (Oesch *et al.*, 1982). In recent years, an epigenetic mechanism for the tumorigenicity of chlorinated hydrocarbon insecticides has become likely in which there is a disruption in intercellular communication—perhaps leading to inhibition of exchange of growth inhibitors (Maslansky and Williams, 1981; Tsushima *et al.*, 1983; Wärngård *et al.*, 1985, 1987, 1988, 1989, Zhong-Xiang *et al.*, 1986). How this would relate to induction of microsomal enzymes, if at all, is not yet clear.

The fact that chlorinated hydrocarbon insecticides and some

other pesticides thought to act by entirely different mechanisms are not additive in their tumorigenic effects may be related to the fact that, whereas all chlorinated hydrocarbon insecticides induce microsomal enzymes, they do so in different ways, as discussed in Section 15.2.2.3. Whatever the reason, the fact remains that the effects are not additive. Experiments in rats were carried out on combinations of Aramite, DDT, methoxychlor, and thiourea (three separate tests) and Aramite, DDT, methoxychlor, and aldrin (Radomski *et al.*, 1965; Deichmann *et al.*, 1967). In the final tests, each compound was fed separately at a dosage corresponding to 50% of its liver tumor-inducing dosage, and four compounds were fed in combination in such a way as to produce a total theoretical tumorigenic dosage of 200%. The authors concluded: "Considering the increased period of survival of rats fed mixtures no. 1 and no. 2 and the lower number of liver tumors produced in these rats, one cannot help but wonder whether the feeding of these mixtures produces an antagonistic type of effect" (Deichmann *et al.*, 1967).

Discussion of Liver Changes in Rodents and Their Possible Significance for Humans In spite of disagreement about interpretation of the liver cell changes, there is general agreement about their development and appearance. The change that can be detected first and can be produced by the smallest effective dosage involves the endoplasmic reticulum. The initial change is reversible but, even more important, it is especially pronounced in rodents. So far, there is no good evidence that anything from the first increase in endoplasmic reticulum to the final development of a highly nodular liver with occasional displacement of cells to the lung can be directly related to the health of humans.

One cannot accept uncritically the high degree of correlation between the ability of compounds to induce parenchymal liver tumors in mice and their ability to induce tumors in the liver and/or other organs of rats and hamsters. As demonstrated by Tomatis *et al.* (1973), this correlation is extremely good for compounds that are or are suspected of being carcinogens in humans but the correlation is poor for chlorinated hydrocarbon insecticides.

All available evidence indicates that humans do not appear to be susceptible to the tumorigenic action of the chlorinated hydrocarbon insecticides and phenobarbital. No increase in the occurrence of tumors has been found in heavily exposed populations. This includes groups of workers who manufacture and formulate DDT, dieldrin, aldrin, endrin, chlordane, and heptachlor and who have been examined carefully for tumors (Laws *et al.*, 1967; Jager, 1970; Vergsteeg and Jager, 1973; van Raalte, 1977; Wang and MacMahon, 1979a,b; Ditraglia *et al.*, 1981; Shindell *et al.*, 1981; Shindell and Ulrich, 1986; Ribbens, 1985).

Studies based on complete tumor registries indicate no increase of liver tumors attributable to phenobarbital among men and women who received heavy, essentially lifelong dosing with this drug for the control of epilepsy (Clemmesen *et al.*,

1974; MacMahon, 1985). In the United States, the total death rates for cancer of the liver and its biliary passages (classified individually as "primary," "secondary," and "not stated whether primary or secondary") lead to the conclusion that there has been a significant, almost constant decrease in the total rate of liver cancer deaths from 8.8 per 100,000 population in 1930 to 8.4 in 1944 (when DDT was introduced) to 5.6 in 1972. This almost constant decline in total liver cancer death rates over 42 years offers no evidence of any increase in liver cancer deaths since the introduction of the first organochlorine pesticide into the environment. The decrease in liver cancer deaths is even more significant in light of the increasing life span of the general population in the United States, which has resulted in an increased percentage of the population at risk from cancer over these years. In spite of the limitation inherent in the interpretation of such data, this record is a reminder that, more than 30 years after the introduction of DDT, there is no evidence whatsoever that DDT is carcinogenic in humans [Deichmann and MacDonald, 1976, 1977; World Health Organization (WHO), 1979; Higginson, 1985].

In the United States, the incidence of cancer is lower in rural counties than in metropolitan areas in general (Mason *et al.*, 1975). Actually, the highest nonoccupational storage of DDT in the United States has been measured in rural situations, largely as a result of local consumption of foods such as eggs that had high residues because of practices involving foods raised for local consumption only.

Sometimes it is implied that epidemiological evidence is useless for revealing the carcinogenicity of a material to humans unless it involves large numbers of people who have been exposed to the material for most or all of a lifetime. The fact is that some human carcinogens have been detected through their occurrence in high incidence in small groups for periods much less than 25 years. What is commonly considered the first recognition of chemical carcinogenesis in humans depended on the observations of a surgeon (Pott, 1775, 1790) in a small fraction of his patients. Such was the intensity of the exposure of the apprentices of chimney sweepers that cancer of the scrotum often appeared at puberty. In connection with tumors of the bladder caused mainly by β -naphthylamine but to a lesser degree by other aromatic amines, Hueper (1942, pp. 496-497) reviewed a series of cases in which the time from first exposure to recognition of symptoms was 8-41, 9-28, and 2-35 years, and in one series of 83 cases 71% of the tumors appeared from 1 to 15 years after exposure. Kleinfeld (1967) reported a 50-76% incidence of bladder cancer among several groups of workers. He also noted a sharp drop in incidence of this condition following decrease—but not discontinuation—of occupational exposure to β -naphthylamine. Thus heavy exposure to aromatic carcinogens may therefore produce cancer quickly. Hepatomegaly and induction of microsomal enzymes caused by chlorinated hydrocarbon insecticides do, however, occur in humans and may be slow to regress (Guzelian, 1985), so that for chemicals of this type other than DDT—for instance, BHC and chlordeneone—it may be too soon to be absolutely sure that they

are of no carcinogenic hazard to humans. For instance, a recent study of DDT, DDE, and β -BHC levels in ear wax collected from 3800 persons in the general populations of 35 Chinese counties showed a significant correlation between β -BHC levels and mortality rates from liver cancer, colon and rectal cancer, and lung cancer in males and colon cancer in females (Wang *et al.*, 1988).

In addition, it is worth remembering that in animals many of these insecticides are good promoters of liver cancer initiated by well-known carcinogens. Some of the areas of the world where DDT and lindane are used in large quantities are also areas where the risk of hepatocellular carcinoma is much greater than in the United States due to aflatoxin contamination of food or to carrying of the hepatitis B virus.

Changes in Nonmicrosomal Enzymes In addition to the important changes in microsomal enzymes caused by various chlorinated hydrocarbon insecticides, changes in nonmicrosomal enzymes have been documented. Among these enzymes are a number involved with gluconeogenesis (Karnik *et al.*, 1981). There is evidence that the first step in this process by DDT, chlordane, endrin, or heptachlor is stimulation of the cyclic AMP–adenylate cyclase system (Singhal and Kacew, 1976).

15.2.3.3 Other Toxic Effects

Besides affecting the liver and the nervous system, chlorinated hydrocarbon insecticides can cause disturbances of function in other tissues of experimental animals. These will be covered in the appropriate sections but include the thyroid (e.g., A. Singh *et al.*, 1985), which may lead to thyroid tumors (IARC, 1974, 1979, 1982, 1983). DDT and analogs have estrogenic effects (see Section 15.3.1.2) and, like the polyhalogenated aromatic chemicals, chlorinated hydrocarbon insecticides can accumulate in adrenals, causing various hormonal changes in the animal (Baggett *et al.*, 1980). Mirex will cause cataracts in fetuses and rat pups from dams treated with the chemical (Gaines and Kimbrough, 1970; Rogers and Grabowski, 1983) and many of these insecticides have effects on the immune system (Descotes, 1986), although whether this causes any adverse effects in the animal is unknown.

15.2.4 DIFFERENTIAL DIAGNOSIS

Poisoning caused by chlorinated hydrocarbon insecticides is acute whether caused by single or repeated doses. Of course, animals may be kept in a state of continuing illness by carefully chosen repeated doses. However, animals that survive recover promptly when dosage is discontinued. The same appears to be true of humans.

Human poisoning following massive accidental or suicidal exposure presents no problem of differential diagnosis. Diagnosis might be difficult if exposure were unrecognized and the

illness so mild that no convulsion occurred. However, any such illness would be brief and without sequel, so a failure of diagnosis would not be too serious.

If the fact of exposure is unrecognized in a case involving one or more convulsions, the differential diagnosis must involve (a) poisoning by a chlorinated hydrocarbon insecticide, (b) poisoning by some other kind of compound, including numerous drugs, (c) epilepsy, (d) convulsions secondary to infection, and (e) convulsions due to toxemia of pregnancy.

If substantial exposure to any chemical is suspected, every effort should be made to obtain samples that could confirm or refute a diagnosis of poisoning. This means that samples of vomit, stomach washings, urine and feces, blood, and food the patient was eating or materials actually used in preparing that food should also be saved for chemical analysis.

When it appears that convulsions are caused by a toxicant but the identity of the material is unknown, some hint of its nature may be obtained by careful observation of the patient. Convulsions caused by chlorinated hydrocarbon insecticides tend to appear early in the course of illness. The patient is unconscious during the convulsion, which resembles an epileptic fit except that no aura is present. The patient is left in a dazed state, but even during this period the vital signs are good, the immediate recovery is striking, and there is only a slight tendency for stimulation to induce a second convulsion. Convulsions caused by strychnine involve far more tonic spasm and opisthotonus than is ordinarily seen in poisoning by chlorinated hydrocarbon insecticides, and patients poisoned by strychnine remain conscious during the attack. Most convulsions associated with poisoning by organic phosphorus compounds occur late in the course of illness and are anoxic in origin. The patient is seriously ill before the convulsions begin, and the vital signs, especially respiration, are of poor quality. Of course, if convulsions continue and the patient's course is downhill, convulsions of any origin may be seen in a person with poor respiratory and cardiac function.

The presence of significant, febrile illness before the onset of convulsions tends to point to a diagnosis of infection. Fever can occur in connection with poisoning by chlorinated hydrocarbon insecticides (see Section 15.2.3.1), but it tends to start after convulsions, not before. Convulsions associated with infection are most common in babies still too young to explore and ingest poisons. In contrast, poisoning is most common between the ages of 1 and 3 years.

Poisoning by DDT is characterized by tremor early in the illness in a way that is not true of other chlorinated hydrocarbon insecticides (see Section 15.3.1.2). With this exception, it is essentially impossible to distinguish between the acute clinical pictures produced by sufficient dosages of the different chlorinated hydrocarbon insecticides without a history of exposure or analytical results.

The only chlorinated hydrocarbon insecticide that has caused chronic poisoning—but apparently no acute poisoning—is chlordeneone, for which the clinical picture is quite different (see Section 15.7.2.3).

15.2.5 TREATMENT OF POISONING IN HUMANS

The treatment of poisoning by a chlorinated hydrocarbon insecticide must be based mainly on general principles and on the results of animal experiments. Limited experience in treating human poisoning offers assurance that proper treatment is beneficial. However, there simply have not been enough properly treated cases of poisoning by chlorinated hydrocarbon insecticides to permit the kind of evaluation of therapy that has been possible in connection with organic phosphorus insecticides.

Whether first attention in a particular case is given to removal of the poison or to sedation must depend on the condition of the patient at the time.

15.2.5.1 Removal of Poison

Of course, the initial dosage of any chlorinated hydrocarbon insecticide should be reduced as rapidly as circumstances permit. The importance of bathing, vomiting, cathartic, and other related procedures has been reviewed (Section 8.2.1), and the importance of supportive treatment has been discussed (Section 8.2.2). Oily laxatives should be avoided because they promote absorption of insecticide or solvent. However, nonabsorbable lipids may be of some use in hindering the absorption of lipophilic toxins including the chlorinated insecticides (Janacek, 1982).

The ability of activated charcoal to absorb dieldrin and some other chlorinated hydrocarbon insecticides and thus promote their excretion in the feces following an acute dose is fully established. A few studies have indicated that activated charcoal (presumably by partially interrupting the enterohepatic circulation) can speed fecal excretion of stored dieldrin after dieldrin intake has stopped (Wilson and Cook, 1970).

Unfortunately, other studies failed to demonstrate any reduction of storage or increase in excretion associated with feeding of large doses of carbon (Fries *et al.*, 1970; Engebretson and Davison, 1971). The reason for the discrepancy in results is not evident. The charcoal used in some tests may not have been truly activated. In view of the proven effectiveness of phenobarbital and some other inducers of microsomal enzymes in speeding storage loss and excretion of several chlorinated hydrocarbon insecticides (Section 7.2.3), one certainly cannot consider successful use of these inducers in combination with charcoal as evidence for the effectiveness of charcoal (Braund *et al.*, 1971; Dobson *et al.*, 1971).

One must conclude that the treatment of people with activated charcoal is harmless, but its value, except in acute poisoning by certain compounds, is unproved in both animals and humans.

Plasmapheresis had no lasting effects on chlordcone levels in the blood of a poisoned patient (Guzelian, 1981) and hemoperfusion over various adsorbents was not an effective treatment, although promising results had been obtained *in vitro*

(Skalsky *et al.*, 1979). Hemoperfusion over XAO-4 has, however, produced promising results in a case of acute poisoning by lindane (Daerr *et al.*, 1985).

Cholestyramine At least one chlorinated hydrocarbon insecticide can be removed from the body selectively by oral administration of an anion exchange resin. Its practical use has been in chronic poisoning, but it should be equally or more effective in acute poisoning.

The fact that some compounds undergo enterohepatic circulation is well recognized (Section 3.2.4.2). This circulation has been demonstrated for several chlorinated hydrocarbon insecticides and probably occurs, for a greater or lesser period, with many or all others. However, it is only in connection with chlordcone that this phenomenon has been turned to therapeutic advantage. Having found evidence that only about 10% of chlordcone excreted in human bile is eliminated in the feces, Cohn *et al.* (1976) administered cholestyramine to seven patients at the rate of 24 gm/person/day for 3 days after having shown that the drug precipitates chlordcone from human bile *in vitro*. The treatment resulted in a 6.7-fold increase in fecal excretion. In 11 of 12 patients given 16 gm/person/day, disappearance of chlordcone from the blood was increased (compared to each person's rate before treatment), and the difference was significant in 7 of them. The average half-life of chlordcone in the blood was reduced from 165 to 80 days (Cohn *et al.*, 1978).

Choice of cholestyramine undoubtedly was based on the fact that it has been used successfully for years to increase the fecal excretion of bile acids, which, like chlordcone, are multiring compounds. The drug has been used in patients with pruritis due to partial biliary obstruction. Such patients have abnormally high levels of bile acids in their blood and tissues. It is thought that severe itching of some of the patients is the result of the high levels of bile acids in their skin.

Cholestyramine has a pH of 5–6. It is quite hydrophilic, but it is not soluble in water and is not hydrolyzed by digestive enzymes. Thus any compound bound to it is excreted with the feces.

Although the value of cholestyramine for promoting the fecal excretion of chlordcone was demonstrated first in people, it was considered prudent to study the matter in rats before using it very long for treating people. The rats received a single oral dose of [¹⁴C]chlordcone at the rate of 40 mg/kg. Cholestyramine produced an increase in the fecal excretion of radioactive material detectable within 24 hr. The total excretion of pesticide in the stool during 2 weeks of treatment was twice that of control animals, and treated animals killed at the end of this period contained 31–52% less radioactivity in different tissues and fluids than was true of the same tissues and fluids in controls (Boylan *et al.*, 1978).

Although chlordcone is the only pesticide whose excretion is known to have been promoted by cholestyramine, one must agree with Guzelian and co-workers (Cohn *et al.*, 1976; Boylan *et al.*, 1978; Guzelian, 1982a), who suggested that it might

be valuable for treating persons poisoned by other chlorinated hydrocarbon pesticides or even other lipophilic substances. Recent evidence showing that sucrose polyester in conjunction with caloric restriction reduced the body content of DDE in gerbils dosed with DDT suggests that this may be an alternative treatment for humans (Mutter *et al.*, 1988).

15.2.5.2 Sedative and Anticonvulsive Therapy

The anticonvulsants that have been used most in treating poisoning by chlorinated hydrocarbon insecticides, in both patients and experimental animals, are pentobarbital and phenobarbital. It must be emphasized here that experiments in animals poisoned by dieldrin suggest that, for treating such poisoning in people, the drugs might have to be given at approximately twice the maximal rates used for other purposes. Such use is entirely safe as long as it achieves its objective of preventing convulsions and calming the patient without producing unconsciousness. Furthermore, it might be necessary to continue dosage with barbiturates at a high rate for 2 weeks or more. However, prolonged treatment has not proved necessary in human cases that have been described. It may be that people discontinue use and seek medical aid when their exposure is less and their illness milder than was true in the animal experiments just mentioned.

The value of barbiturates for promoting increased metabolism of chlorinated hydrocarbon insecticides remains unchallenged, and their use, even for this purpose alone, probably ought to continue. However, there is growing evidence for the use of diazepam for the control of convulsions. It is now regarded as the drug of choice for treating status epilepticus [American Medical Association (AMA), 1986]. It also has been used for treating convulsions caused by drugs and toxins. Experience in its use for treating poisoning by chlorinated hydrocarbon insecticides is limited.

The usual anticonvulsant dose of diazepam for adults is 5–10 mg administered slowly, intravenously. If convulsions make intravenous injection difficult, intramuscular injection may be substituted. Up to 10 mg/day may be given orally for maintenance. After convulsions have been controlled, diazepam should be discontinued gradually over a period of 2 or 3 days.

In at least two cases, paralysis combined with artificial respiration proved effective when anticonvulsants had failed. When endrin convulsions persisted every 15–20 sec in a 2-year-old girl in spite of large doses of phenobarbital, pentobarbital, and chloral hydrate, she was paralyzed by succinylcholine (0.5–1 mg/min, iv for 24 hr) while being maintained by mechanically assisted respiration with humidified 40% oxygen. Respiratory assistance was discontinued after an additional 8 hr. Improvement was gradual over a period of several days; recovery was complete (Hayden *et al.*, 1965).

Another case involved a 21-year-old man who ingested dieldrin at the rate of 120 mg/kg. Unconsciousness, cyanosis, and fits occurred before treatment was possible. An endotracheal tube was passed and gastric lavage was performed, but only a negligible amount of dieldrin was recovered. Mannitol (200 ml

of a 20% solution) was left in the stomach to induce catharsis. Metoclopramide (10 mg) was administered intravenously. A total of 60 mg of diazepam was given intravenously to control convulsions. The patient was then transferred to another hospital where more definite treatment was possible. When he arrived there 3.5 hr after ingesting dieldrin, he was still unconscious; his pulse was 120/min and his blood pressure was 180/120 mm Hg. There was no focal neurological deficit, but he had further convulsions while undergoing assessment, and he was given an additional 20 mg of diazepam. However, in the intensive care unit, profound muscular paralysis with pancuronium bromide was necessary before convulsions could be controlled sufficiently to allow adequate intermittent positive pressure ventilation. The paralysis was maintained for 48 hr before being withdrawn gradually, and it was supplemented with conventional anticonvulsive agents (phenobarbital 200 mg every 4 hr intramuscularly and phenytoin 100 mg every 6 hr, with 10-mg doses of diazepam intravenously as necessary). Intermittent positive pressure ventilation was used for 3 days. The rapid pulse and high blood pressure were considered due to sympathetic overactivity; 5 hr after admission, 10 mg of propranolol intravenously reduced the pulse rate to 100/min and the blood pressure to 130/90 mm Hg. Propranolol (10 mg orally, every 6 hr) was administered for a further 60 hr to maintain a degree of β -sympathetic blockade. Rectal temperature remained between 38 and 39°C for much of the first 48 hr despite surface cooling by fanning and evaporation. On day 5, the patient was transferred to a general medical ward, but anticonvulsive medication was maintained for another 2 days. Poor memory and some persistent headaches were the patient's only complaints when he was seen on days 10 and 24. In spite of his bland affect at this time, he was severely disturbed psychologically, but whether this was the cause or effect of his self-poisoning was uncertain (Black, 1974).

Other sedatives (paraldehyde and chloral hydrate) have been used in cases of poisoning in humans with apparent benefit. However, there is no experimental evidence indicating that they are equal or superior to barbiturates.

Calcium gluconate is reported to control convulsions in experimental animals caused by some chlorinated hydrocarbon insecticides. It has appeared helpful in a few human cases. Since the mechanism of action is entirely different, it may be used in addition to sedatives and anticonvulsants.

Epinephrine is contraindicated. It sensitizes the heart, predisposing to serious arrhythmias and thus to death.

Regardless of what pharmacological antidote may be used, attention must be given as required to the general care of the patient (Section 8.2.2.9), use of oxygen (Section 8.2.2), maintenance of the airway, and artificial respiration (Section 8.2.2.1) if required.

Sometimes the insecticides may be used as solutions in organic solvents. The toxicity of the solvent should of course also be taken into account if a poisoning of this kind occurs. Jaeger *et al.* (1984) have reported six cases of poisoning by lindane–solvent mixtures. Diazepam was sufficient to control convulsions in five cases but vomiting and pulmonary edema in

some of the patients was thought to be due to the solvent (benzene) and not to lindane.

15.3 DDT AND ITS ANALOGS

15.3.1 DDT

DDT came to widespread attention because it dramatically controlled typhus and malaria in time of war. When it became available for civilian use, it controlled flies and other pests that annoy large numbers of people and may transmit disease, and it increased the production of important crops. Knowledge that traces of it are stored in essentially everyone in the world kept DDT in the spotlight. Later it was implicated in the injury of a wide variety of wildlife. Under these circumstances it is no wonder that DDT has been studied more thoroughly than any other pesticide and in more diverse relationships than any drug. By necessity, information on DDT was used to illustrate many principles and concepts discussed in Volume 1, including some very important matters such as human exposure levels and effects on domestic and wild animals that are not touched on in the present volume. In the following discussion some other subjects including details of storage and excretion of DDT in humans are covered, and there remains much to say about this fascinating compound.

15.3.1.1 Identity, Properties, and Uses

Chemical Names *p,p'*-DDT, in Chemical Abstracts, is 1,1'-(2,2,2-trichloroethylidene)-bis(4-chlorobenzene). Common nomenclatures that have been used are 1,1,1-trichloro-2,2-

bis(*p*-chlorophenyl)ethane, 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane, and 1,1-bis(4-chlorophenyl)-2,2,2-trichloroethane. Because the older terminology has been used so widely in the past and many abbreviations are based on it (e.g., *p,p'*-DDT and *o,p'*-DDT), the *o* and *p* nomenclature will be used in this chapter for referring to DDT in its abbreviated form.

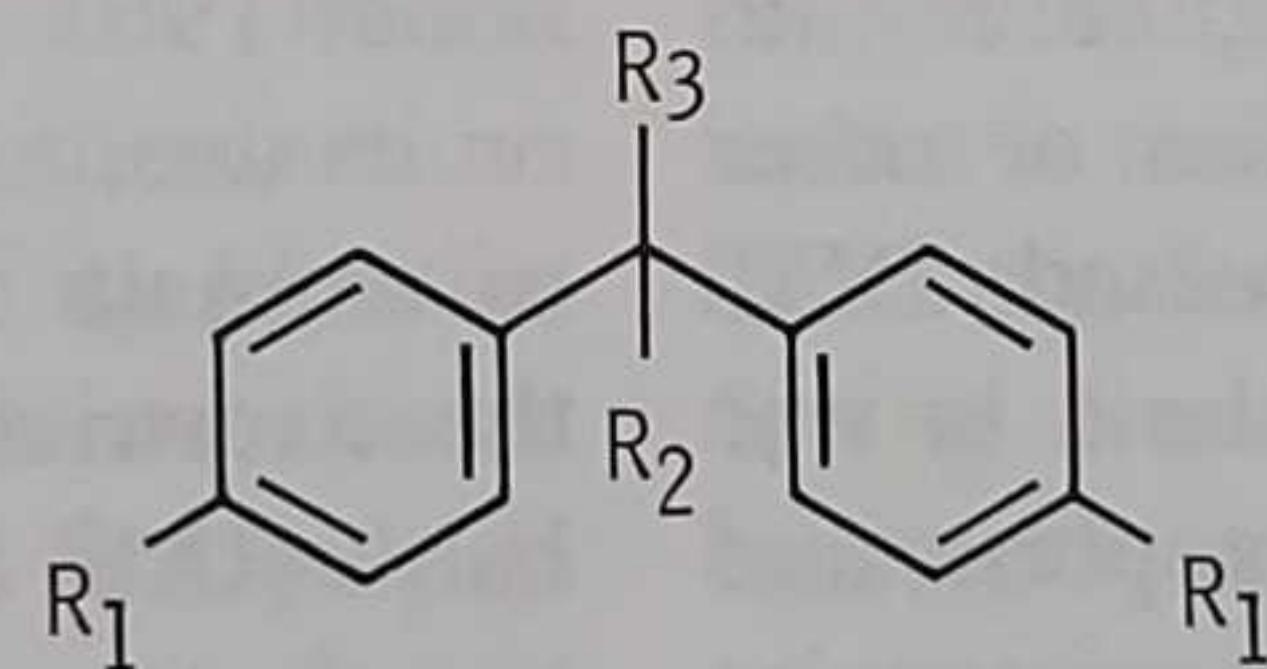
Structure The structure of *p,p'*-DDT and the structures of several of its analogs are shown in Table 15.2. The table is confined to compounds that occur in commercial DDT and analogs that have had some use as insecticides. It must be emphasized that even the commercially available insecticidal analogs have strikingly different properties. Especially remarkable are the slow metabolism and marked storage of DDT and its metabolite DDE and the rapid metabolism and negligible storage of methoxychlor.

No attempt has been made to include in Table 15.2 the tremendous range of compounds that have been synthesized and studied in connection with structure-activity relationships, often with the hope of emphasizing the good properties of DDT and reducing its undesirable properties. For a more extensive consideration of analogs, see Metcalf (1973).

The formation of metabolites is considered under the heading Metabolism in Section 15.3.1.2.

Synonyms DDT apparently is universally accepted as the common name of the insecticide identified above. The term has been in use longer than official agencies for approving common names have existed or at least longer than these agencies have shown an interest in pesticides. As approved by BSI, DDT refers to the technical product, and there is historical

Table 15.2
Structure of *p,p'*-DDT and a Few of Its Analogs That Have Had Commercial Use



Name	Chemical name ^a	R ₁	R ₂	R ₃
DDT	1,1,1-trichloro-2,2-bis(4-chlorophenyl) ethane	Cl	H	Cl ₃
Bulan ^b	2-nitro-1,1-bis(4-chlorophenyl) butane	Cl	H	CH(NO ₂)CH ₂ CH ₃
chlorfenethol (DMC)	1,1-bis(4-chlorophenyl) ethanol	Cl	OH	CH ₃
chlorobenzilate	ethyl 4,4'-dichlorobenzilate	Cl	OH	COOCH ₂ CH ₃
chloropropylate	isopropyl 4,4'-dichlorobenzilate	Cl	OH	COOCH(CH ₃) ₂
DFDT	1,1,1-trichloro-2,2-bis(4-fluorophenyl) ethane	F	H	CCl ₃
dicofol (Kelthane [®])	2,2,2-trichloro-1,1-bis(4-chlorophenyl) ethanol	Cl	OH	CCl ₃
ethylan (Perthane [®])	1,1-dichloro-2,2-bis(4-methoxyphenyl) ethane	CH ₂ CH ₃	H	CHCl ₂
methoxychlor	1,1,1-trichloro-2,2-bis(4-methoxyphenyl) ethane	OCH ₃	H	CCl ₃
Prolan ^b	2-nitro-1,1-bis(4-chlorophenyl) propane	Cl	H	CH(NO ₂)CH ₃
TDE ^c	1,1-dichloro-2,2-bis(4-chlorophenyl) ethane	Cl	H	CHCl ₂

^a See Section 15.3.1.1, Chemical Names. The names used here are those which are commonly encountered.

^b A mixture of Prolan and Bulan (1:2) has been sold in the past as Dilan[®].

^c As an insecticide, this compound has the approved name of TDE; as a metabolite of DDT it usually is called DDD. It has been sold under the name

Rhothane[®]; as a drug, the *o,p'*-isomer is called mitotane.

justification for that practice because DDT is an acronym for dichlorodiphenyltrichloroethane. *p,p'*-DDT is approved by BSI as a separate term. Zeidler (1874) called the compound di-monochlorophenyltrichloräthan. When used as a drug, DDT is known in the United Kingdom as dicophane (BP), in Sweden as klorfenoton, and in the United States as chlorphenothane (USP).

DDT has been sold under a variety of trade names, including Anofex®, Cesarex®, Didimac®, Digmar®, Dinocide®, Genitox®, Guesarol®, Gyron®, Ixodex®, Neocid®, and Zerdane®. Code designations for DDT include OMS-16 and ENT-1,506. The CAS registry number for *p,p'*-DDT is 50-29-3.

Physical and Chemical Properties DDT has the empirical formula $C_{14}H_9Cl_5$ and a molecular weight of 354.49.

Pure *p,p'*-DDT is a white, tasteless, almost odorless crystalline solid melting at 108.5 to 109.0°C. Technical DDT is a waxy solid.

A typical example of technical DDT had the following composition: *p,p'*-DDT, 77.1%; *o,p'*-DDT, 14.9%; *p,p'*-DDD, 0.3%; *o,p'*-DDD, 0.1%; *p,p'*-DDE, 4.0%; *o,p'*-DDE, 0.1%; and unidentified compounds, 3.5%. The vapor pressure of DDT is 1.5×10^{-7} mm Hg at 20°C. DDT is highly soluble in apolar organic solvents: solubility per 100 ml acetone, 58 gm; ethanol, 2 gm; benzene, 106 gm; carbon tetrachloride, 45 gm; cyclohexanone, 116 gm; ethyl ether, 28 gm; petroleum ethers and kerosene, 4–10 gm. It is practically insoluble in water.

History DDT was first synthesized by Zeidler (1874). However, it was put to no use until its insecticidal properties were discovered by Paul Müller in 1939. The Swiss patent was issued in 1942.

The first sample sent to the United States arrived there in September 1942. This sample was tested for effectiveness and safety. The results were so encouraging that manufacture was given high priority. At first, the entire production was used for the protection of troops against malaria, typhus, or certain other vector-borne diseases, or against biting flies or other insects that are merely pests. As the supply increased, DDT was used in the United States for control of malaria in war areas, that is, in the vicinity of military installations, ports, and transportation centers. As a result of this effort, mosquito transmission of malaria was brought to an end in the United States in 1953, even though military personnel and other infected persons from the tropics continued to reintroduce the disease extensively as late as 1972 and in diminishing numbers thereafter.

The revolution in the control of malaria and typhus among allied troops and among certain civilian populations during World War II was accomplished with relatively little DDT. Far greater amounts were required for the control of agricultural and forest pests that became possible after the compound was released in the United States for commercial use on August 31, 1945. Civilian use in other countries became possible a little later, first largely on the basis of importation and gradually on the basis of local manufacture.

Formulations and Production Technical DDT has been formulated in almost every conceivable form including solutions in xylene or petroleum distillates, emulsifiable concentrates, water-wettable powders, granules, aerosols, smoke candles, charges for vaporizers, and lotions. Aerosols and other household formulations often are combined with synergized pyrethrins.

Production and use of DDT in the United States have been discussed in Section 1.5.

Quantities of DDT and related compounds used in or sold for agricultural purposes in various countries in 1970 were as follows (tonnes): Australia (1000.0), Austria (20.5), Botswana (2.0), Canada (287.0), Ceylon (16.6), Columbia (980.0), Czechoslovakia (270.0), Egypt (3457.0), El Salvador (466.0), Federal Republic of Germany (152.0), Finland (6.1), Ghana (0.3), Guatemala (380.0), Hungary (20.6), Iceland (0.3), Israel (10.0), Italy (2178.0), Japan (401.0), Khmer (46.8), Kuwait (0.2), Madagascar (176.0), Ryukyu Islands (0.3), Sudan (269.0), Upper Volta (1.5), and Uruguay (5.0) [Food and Agriculture Organization (FAO), 1972]. These values total 10,146.2 tonnes. Thus, at least until 1970 the use of DDT was extensive on a worldwide basis but varied greatly from one country to another. A worldwide production of 60,000 tonnes for 1974 has been estimated (WHO, 1979), but there do not appear to be any figures for DDT production since then.

Changing Patterns of Use Before 1945, all of the DDT produced in the United States was used or allocated by the military services for various medical and public health uses. Early in 1945 it became available for rather extensive experimental work in agriculture, and it was commercially available in limited quantities early in the autumn of the same year (U.S. Department of Agriculture, 1945a,b). The results were so spectacular that use increased until 1959. In response to a demand for exports, production continued to increase until about 1963. Even before 1963 some restrictions were placed on its use, mainly to minimize residues in food and in the feed of animals that produce milk and meat. Among the first of these restrictions was that on its use on dairy cattle or in dairy barns (U.S. Department of Agriculture, 1949). Another important factor reducing the use of DDT was the increasing resistance of pests. One of the first species to be affected was the housefly; because of its abundance and widespread distribution, its resistance was bound to be noticed by the public generally. Although many pests of public importance have been resistant to DDT in some or all of their range, resistance among vectors of malaria has been minimal. Because malaria control constitutes such a large segment of vector control, the use of DDT for vector control has tended to remain stable, while its use in agriculture continued to decline, especially in temperate climates.

When Sweden banned DDT in March 1969 (to become effective January 1, 1970), they did so objectively, pointing out that "the need for insecticides is rather small in Sweden compared to that in many other countries" and that the ban of this

and certain other chlorinated hydrocarbon insecticides could be used as a tool to explore scientific problems about their movement in the environment. The safety of the chlorinated hydrocarbon insecticides under actual conditions of use was emphasized (Hayes, 1969).

In order to respond to ecologists who considered that the widespread occurrence of DDT in the environment was inherently bad and was the direct cause of injury to certain fish and birds, government agencies of some other countries attempted to justify restrictions on the use of DDT by its alleged threat to human health. This did not prevent the same agencies from providing that DDT might be used, if needed, to combat any future threat from vector-borne disease within their boundaries.

As the situation now stands, although many countries severely restrict the use of DDT, it is still used extensively, for both agriculture and vector control, in some tropical countries. Information apparently is not available on how much of the agricultural use involves food protection or how much loss of food production would result if use of DDT were discontinued. How much of the use of DDT is in public health is also unknown, but the picture with malaria control is clear. According to WHO in 1971, substitution of malathion or propoxur for DDT would increase the cost of malaria control approximately 3.4- and 8.5-fold, respectively, and this increase could not be supported in some countries without a decrease in the coverage of control programs. If DDT were not used, vast populations in the malarious areas of the world would be condemned to the frightening ravages of endemic and epidemic malaria (WHO, 1979).

15.3.1.2 Toxicity to Laboratory Animals

Symptomatology The description of DDT intoxication in animals given by Domenjoz (1944) remains one of the best. The first perceptible effect is abnormal susceptibility to fear, with violent reaction to normally subthreshold stimuli. There is definite motor unrest and increased frequency of spontaneous movements. As poisoning increases, hyperirritability like that seen in strychnine poisoning develops, but convulsions do not appear at this time. A fine tremor, recognizable at first only as a terror reaction, is later present as an intention tremor in connection with voluntary movement, is then present intermittently without observable cause, and is finally present as a coarse tremor without interruption even for several days. Spontaneous movement is limited, and food intake stops so that surviving animals lose weight. In the later stages, especially in some species, there are attacks of epileptiform, tonic-clonic convulsions with opisthotonus.

All the signs are strengthened by external stimuli and become manifest at first through external stimuli. In all stages, the animals show normal position and labyrinth reflexes. The picture of poisoning in mammals recalls the disturbances of movement and tone that are known in human pathology as the amyostatic syndrome.

Symptoms appear several hours after oral administration of

the compound, and death follows after 24–72 hr. The latent period after intravenous administration at about the LD₅₀ level is approximately 5 min; signs of poisoning reach a maximal level in about 30 min, and survivors are symptom-free in 18–24 hr. Animals that survive recover completely.

In addition to the features of poisoning already mentioned, Cameron and Burgess (1945) noticed that as rats, guinea pigs, and rabbits become sick they become cold to the touch and show ruffled fur. Some show diarrhea. These authors found that muscular tremors were preceded by muscular weakness which occurred first in the back and later in the hind legs. The front legs were relatively spared so that animals showing marked weakness of the hindquarters could still drag themselves about. However, several authors have found that the tremor characteristic of DDT poisoning generally starts in the muscles of the face, including the eyelids, and spreads caudally with variable severity until all the muscles are affected. Furthermore, although weakness of hindquarters has been seen by others, it is not a common finding.

Although there is a general similarity in the clinical effects of DDT in all vertebrate species, some characteristic differences exist. Cats show greater extensor rigidity and opisthotonus than other laboratory animals. The stiffness appears first in the distal part of the extremities and later extends to the proximal part and to the trunk. Poisoned cats show marked pilomotor activity. Convulsions in them may become almost continuous. Convulsions are also prominent in dogs, as is ataxia. Tremors are so pronounced in rats that it may be difficult to detect clonic convulsions in them. Rats poisoned by DDT show a reddish color about the eyes. The color has been attributed to excessive secretion of a porphyrin by the harderian glands and can occur when rats are ill from many other causes.

Poisoning produced by repeated doses of DDT differs from that produced by a single dose only insofar as the animal may be gradually debilitated, especially by malnutrition. If food intake is maintained, tremor may last for weeks or even, intermittently, for months. If the animals survive a short time after dosing stops, recovery is complete. However, food intake may be interfered with in at least two ways. Tremor and more severe signs may interfere mechanically with eating. Animals offered food containing high concentrations of DDT often eat little or nothing and lose weight rapidly. However, the same animals will show excellent appetites when offered the same kind of food containing no DDT just after refusing the major portion of their daily ration of contaminated food. Unlike dieldrin and some other compounds, DDT seems to have little effect on appetite as mediated by the central nervous system; it has a great deal to do with taste.

Animals that have suffered severe weight loss as a result of DDT poisoning may die partly as a result of general debility. At least in some colonies they have become prey to secondary infection.

In summary, animals that die as the result of repeated large doses of DDT and small animals that die as a complication of

Table 15.3
Acute Oral and Dermal LD 50 of DDT to Animals^a

Species	Formulation	Oral (mg/kg)	Dermal (mg/kg)
Rat	water suspension or powder	500–2500	1000
	oil solution	113–450	250–3000
Mouse	water suspension or powder	300–1600	375
	oil solution	100–800	250–500
Guinea pig	water suspension or powder	2000	1500
	oil solution	250–560	1000
Rabbit	water suspension or powder	275	375
	oil solution	300–1770	300–2820
Dog	water suspension or powder	>300	
	oil solution		
Cat	water suspension or powder	100–410	

^a Modified from Hayes (1959a).

starvation following many somewhat smaller doses of DDT show the same signs as those seen in animals killed by one or a few large doses. Even though severely ill, animals that survive a few days after the last of many doses of DDT go on to recovery.

Response to a Single Dose Table 15.3 summarizes the acute oral and dermal toxicity of DDT to common laboratory animals, and Table 15.4 summarizes the subcutaneous, intravenous, and intraperitoneal toxicity. Both tables are condensed from an earlier review (Hayes, 1959a), which gives references and additional details. The values include those of Gaines (1960). It may be concluded that dissolved DDT is absorbed by

Table 15.4
Acute Subcutaneous, Intravenous, and Intraperitoneal LD 50 of DDT to Common Laboratory Animals^a

Species	Formulation	Subcutaneous (mg/kg)	iv (mg/kg)	ip (mg/kg)
Rat	water suspension or powder	>2000		
	oil solution	200–1500	47	80–200
Mouse	water suspension or powder	1000–1500		
	oil solution	300		
Guinea pig	water suspension or powder			
	oil solution	900		150
Rabbit	water suspension or powder			
	oil solution	250–>3200	30–41	<2100
Dog	water suspension or powder			
	oil solution		68	
Cat	water suspension or powder			
	oil solution	<650	32	
Monkey	water suspension or powder			
	oil solution		55	

^a Modified from Hayes (1959a).

all portals, although DDT powder is absorbed through the skin to only a negligible degree. It is frequently impossible to put enough DDT dust on the skin of animals to kill them, so that an LD 50 value for this formulation cannot be determined by the dermal route. Although formulation is important in determining the toxicity of DDT by other routes, the difference is not so great as it is in connection with skin exposure. In round figures, DDT is about 4 times more toxic when given intravenously than when given orally and about 40 times more toxic intravenously than dermally.

In general, DDT, like some other lipophilic chemicals, appears more toxic orally as a solution in vegetable oil or animal fat than when given in some petroleum fractions. Petroleum may act as a laxative. The heavier fractions are never absorbed, and DDT dissolved in such fractions has to be extracted from the solvent in order to show toxicity.

In summary, DDT is a compound of moderate acute toxicity. Compared with other chlorinated hydrocarbon insecticides of equal or greater toxicity, it is remarkable in being little absorbed by the skin.

Acute oral LD 50 values of DDT metabolites commonly found in tissues or excreta are shown in Table 15.5. Readily absorbable formulations of the metabolites are less toxic than the most absorbable preparations of the parent compounds (cf. Table 15.3).

At an oral dosage of 150 mg/kg, *p,p'*-DDT produces severe illness in all rats and kills about half of them, but *o,p'*-DDT at the same dosage produces no illness, even though the concentrations of the two compounds in the brain at various intervals after dosing are about the same. At a dosage of 3000 mg/kg, *o,p'*-DDT produces mild to moderate illness, and the concentration in the brain is 5–9 times the concentration of *p,p'*-DDT necessary to produce similar symptoms. Thus, *p,p'*-DDT appears to be inherently more toxic than the *o,p'* isomer (Dale *et al.*, 1966a).

Table 15.5
Oral LD 50 Values of Metabolites of DDT

Compound and species	LD 50 (mg/kg)	Reference
DDE ^a		
rat, M	880	Gaines (1960)
rat, F	1240	Gaines (1960)
mouse	700	von Oettingen and Sharpless (1946)
mouse	1000	Domenjoz (1946a,b)
DDD ^b		
rat, M	>4000	Gaines (1969)
DDA ^c		
rat	1900	Smith <i>et al.</i> (1946)
rat, M	740	Gaines (1960)
rat, F	600	Gaines (1960)
mouse	720	von Oettingen and Sharpless (1946)
mouse	590	Domenjoz (1946a,b)

^a 1,1-Dichloro-2,2-bis(4-chlorophenyl)ethylene.

^b 1,1-Dichloro-2,2-bis(4-chlorophenyl)ethane.

^c 2,2-Bis(4-chlorophenyl)acetic acid.

Table 15.6
Effect of Age on the Toxicity of DDT to Rats

Number of doses	Age ^a	LD 50 (mg/kg) ^b	Reference
1	newborn	>4000	Lu <i>et al.</i> (1965)
1	newborn	2356	Harrison (1975)
1	10 days	728	Henderson and Woolley (1969)
1	14–16 days	437	Lu <i>et al.</i> (1965)
1	weanling	355	Lu <i>et al.</i> (1965)
1	2 months	250	Henderson and Woolley (1969)
1	2 months	152	Mitjavila <i>et al.</i> (1981a)
1	3–4 months	194	Lu <i>et al.</i> (1965)
1	middle-aged	235	Lu <i>et al.</i> (1965)
1	adult	225	Harrison (1975)
4	preweaning	279	Lu <i>et al.</i> (1965)
4	adult	285	Lu <i>et al.</i> (1965)

^a Data from more than one strain of rat.

^b Total intake of one or more doses.

Rats tolerate higher tissue levels of DDA than of DDT. Eighteen hours after intravenous injection of DDA at a rate of 100 mg/kg, tissue levels still were higher than are usually found in animals fatally poisoned by DDT (Judah, 1949). DDA produces somewhat less injury than DDT to the liver but, especially at high intravenous dosages, produces greater damage to the kidney (Lillie *et al.*, 1947). This is consistent with the finding of Spicer *et al.* (1947) that, following administration of DDT, DDA constitutes a higher proportion of DDT-related compounds in the kidney (25%) than in any other tissue, being 12% in the liver, 10% in the brain, and even less in other tissues.

Young animals eat more than adults in relationship to their body weight. For this and other reasons, young animals often are more susceptible than adults to poison in food. However, young animals are inherently less susceptible to certain compounds. There is no evidence that DDT is more toxic to young animals of any species, including humans, and in the rat the young are less susceptible to a single dose (Table 15.6). They are about equally susceptible to repeated doses, as shown in the same table. According to Henderson and Woolley (1969), the relative insusceptibility of the young is associated with relatively poor absorption of DDT by their central nervous systems and by lesser inherent susceptibility of the young brain to DDT already absorbed by it. Further study by the same authors (Henderson and Woolley, 1970) showed that fatal poisoning of both 10- and 60-day-old rats involves hyperexcitability and intense tremor followed by prostration and eventual respiratory failure. However, in the adult rat, DDT causes convulsions, an increase in respiration and heart rate, and a lethal increase in body temperature (40–42°C) prior to death, but the body temperature of the immature rat decreases during acute intoxication by DDT. The authors suggested that, whereas DDT is a direct depressant of respiration in both young and old rats, the additional toxic responses manifested by seizures and hyperthermia account for the increased lethality of DDT in mature animals. No acute LD 50 could be

established for hamsters (Agthe *et al.*, 1970), which also seem resistant to chronic effects of DDT (Table 15.7).

There is virtually no sex difference in the acute toxicity of DDT to rats; the LD 50 is 113 and 118 in males and females, respectively (Gaines, 1960). A similar situation is observed with mice (Agthe *et al.*, 1970). When DDT is fed to rats at ordinary dietary levels, the two sexes store it equally. However, at higher dosages, females store more of the compound; the difference is explained mainly by the lesser activity of the liver microsomal enzymes in female rats and only in part by relatively higher food intake of the females.

Response to Repeated Doses The effects of repeated doses of DDT are summarized in Table 15.7.

The 90-dose oral LD 50 of technical DDT in rats is 46.0 mg/kg/day (Gaines, 1969). The chronicity index is 5.4. Thus the compound has only a moderate tendency to cause cumulative effects, and this limited tendency is fully explained by the accumulation of DDT itself in tissues as a result of continuing intake. In fact, this accumulation, which is strictly dosage dependent, is detectable at all measurable levels of intake. The relationship in humans is shown in Fig. 7.4.

If storage is considered undesirable *per se*, then DDT is without a no-injurious-effect level. However, the same may be said for all compounds that are absorbed, for the presence of all of them in the bodies of exposed organisms—perhaps at very low levels and for relatively short periods—may be assumed; failure to demonstrate low levels of storage does not depend on physiology but only on limitations of the analytical techniques employed.

A number of papers have reported no-effect levels for DDT within parameters other than storage, namely: rat, 0.05 mg/kg/day (Lehman, 1951, 1952); dog, 8 mg/kg/day (Lehman, 1951, 1952); and monkey, 2.2–5.54 mg/kg/day (Dudham *et al.*, 1963).

There remain reports of effects in animals at the lowest dosages investigated. For example, decreased serum albumin and increased β - and α -globulins in the blood of rats and rabbits maintained on a dosage of 0.2 mg/kg/day for 3–11 months were reported by Kagan *et al.* (1969), but these changes are unconfirmed.

In summary, the lowest dosages that have been studied in animals are of the same order of magnitude as those encountered by people who make or formulate DDT and, therefore, hundreds of times greater than the dosages encountered by ordinary people. The animal studies have continued long after a steady state of storage has been achieved. The results permit the conclusion that bioaccumulation sufficient to produce neurotoxicity or other clinical effects, including a reduction of the life span, can occur only at dosage levels substantially higher than those encountered by the most heavily exposed workers. DDT dosages encountered by workers produce in some groups of mice and rats a small but detectable increase of the liver changes (hypertrophy, margination, and liposomes) characteristic of rodents. The same changes occur in low incidence in control mice and rats but not in other animals.

Table 15.7

Effect on Various Animals of Prolonged Oral Administration of DDT

Dosage

Range (mg/kg/day)	Method and concentration (ppm)	Species, ^a number, and sex	Maximum duration	Results	References
41–80	800 ppm in diet	rat	2 yr	increased mortality, typical liver changes, and liver carcinomas hepatomas in 51 and 21% of M and F compared with 18 and 0.6% of controls	Fitzhugh and Nelson (1947) ^b
	46 mg/kg, then 140 ppm in diet	mouse 36 M, 36 F	1.5 yr	no liver tumors and survival slightly less than controls	Innes <i>et al.</i> (1969)
	1000 ppm in diet	hamster 25 M, 30 F	1.9 yr	no liver tumors but decreased serum cholinesterase	Agthe <i>et al.</i> (1970)
	1000 ppm in diet	hamster 30 M, 30 F	1.5 yr	no liver tumors and survival as controls	Graillot <i>et al.</i> (1975)
	1000 ppm in diet	hamster 35 M, 36 F	2.4 yr	100% mortality; liver damage, no tumors	Rossi <i>et al.</i> (1983)
	3200 ppm in diet	dog 10	4 yr	100% mortality	Lehman (1951–1952; 1965)
	5000 ppm in diet	monkey 1 M	10 wk	100% mortality	Durham <i>et al.</i> (1963)
	50 mg/kg/day	monkey 6	14 wk	100% mortality; no hematologic effects	Cranmer <i>et al.</i> (1972)
	400 ppm in diet	rat 24 M, 12 F	2 yr	increased mortality, typical liver changes	Fitzhugh and Nelson (1947) ^b
	500 ppm in diet	rat 37 M, 35 F	2.9 yr	liver tumors in 45%	Rossi <i>et al.</i> (1977)
21–40	500 ppm in diet	rat 38 M, 38 F	2.3 yr	liver tumors in 18% F	Cabral <i>et al.</i> (1982b)
	250 ppm in diet	mouse 103 M, 90 F	2 gen	risk of liver tumor increased 3.7- and 18.5-fold in M and F, respectively	Tomatis <i>et al.</i> (1972)
	250 ppm in diet	mouse 31 M, 121 F	2 gen	liver tumors in 48 and 59% of M and F	Terracini <i>et al.</i> (1973)
	500 ppm in diet	hamster 39 M, 40 F	1.7 yr	no liver tumors and survival as controls	Cabral <i>et al.</i> (1982a)
	2000 ppm in diet	dog 4	4 yr	25% mortality; minor liver damage but no tumors	Lehman (1951–1952; 1965)
	100 ppm in diet	mouse 100 M, 100 F	2 yr	hepatomas increased in F of one strain but no increase in hepatocarcinomas	Fitzhugh (1970)
	100 ppm in diet	mouse 30 M, 30 F	2 yr	risk of liver tumors increased 4.4-fold	Walker <i>et al.</i> (1973)
	100 ppm in diet	mouse 30 M, 3 F	2 yr	risk of liver tumors increased 3.3- and 4.2-fold in M and F	Thorpe and Walker (1973)
	50 ppm in diet	mouse 127 M, 104 F	2 gen	risk of liver tumors increased 2.45- and 3.46-fold in M and F, respectively	Tomatis <i>et al.</i> (1972)
	50 ppm in diet	mouse 30 M, 30 F	2 yr	Risk of liver tumors increased 2.9-fold	Walker <i>et al.</i> (1973)
6–10	400 ppm in diet	dog 2	4 yr	no effect	Lehman (1951–1952; 1965)
	20 ppm in diet	mouse 48 M, 128 F	2 gen	no increase in tumors	Terracini <i>et al.</i> (1973)
	200 ppm in diet	monkey	7.5 yr	no effect	Durham <i>et al.</i> (1963)
1.26–2.5	10 ppm in diet	mouse 104 M, 124 F	2 gen	risk of liver tumors increased 2.26- and 2.46-fold in M and F, respectively	Tomatis <i>et al.</i> (1972)
	25 ppm in diet	rat	2 yr	no clinical effect; M survived longer than controls	Treon and Cleveland (1955)
0.31–0.63	10 ppm in diet	rat	2 yr	typical liver changes; no effect on reproduction	Fitzhugh (1948)
	12.5 ppm in diet	rat	2 yr	no effect	Treon and Cleveland (1955)

(continued)

Table 15.7 (Continued)

Dosage	Method and concentration (ppm)	Species, ^a number, and sex	Maximum duration	Results	References
0.16-0.31	2.8-3.0 ppm in diet	mouse 683	5 gen	tumors in 28.7%, including lung carcinomas, lymphomas, and leukemias	Tarján and Kemény (1969)
	2 ppm in diet	mouse 124 M, 111 F	2 gen	risk of liver tumor doubled in M, unchanged in F	Tomatis <i>et al.</i> (1972)
	2 ppm in diet	mouse 58 M, 135 F	2 gen	no increase in tumors	Terracini <i>et al.</i> (1973)
0.08-0.16	2.5 ppm in diet	rat	2 yr	no effect	Treon and Cleveland (1955)

^a Various strains of rats were used; Osborne-Mendel (Fitzhugh and Nelson, 1947), Carworth (Treon and Cleveland, 1955), Wistar (Rossi *et al.*, 1977), MRC-Porton (Cabral *et al.*, 1982b). Mouse strains used were (C57BL/6 × C3H/Anf)Fl and (C57BL/6 × AKR)Fl (Innes *et al.*, 1969), CFL (Tomatis *et al.*, 1972; Thorpe and Walker, 1973; Walker *et al.*, 1973), BALB/cJ and C₃HeB/FeJ (Fitzhugh, 1970), BALB/c (Tarján and Kemény, 1969; Terracini *et al.*, 1973).

^b Slides reexamined by Reuber (1978).

Absorption Most DDT dust is of such large particle size that any that is inhaled is deposited in the upper respiratory tract and eventually is swallowed (see Section 3.2.2.4). Toxicity data indicate that respiratory exposure to DDT is of no special importance.

Review of the early literature indicates that the absorption of DDT from the gastrointestinal tract is slow. Whereas intravenous injection at the rate of 50 mg/kg produces convulsions in rats in 20 min, convulsions occur only after 2 hr when DDT is administered orally at a rate two or more times the LD₅₀ value. The onset of convulsions is delayed for about 6 hr when DDT is given to rats orally at approximately the LD₅₀ value (Dale *et al.*, 1963).

Early studies based on toxicity indicated that DDT dissolved in animal or vegetable fats is absorbed from the gastrointestinal tract about 1.5-10 times more effectively than is undissolved DDT. This has been confirmed in a number of studies, e.g., Keller and Yeary (1980) and Palin *et al.* (1982). There was also evidence that large doses of the compound in the gastrointestinal tract were poorly absorbed from nonabsorbable solvents. At high dosage levels, less [¹⁴C]DDT is absorbed and stored in organs following oral than following intraperitoneal administration, and a higher proportion is excreted in the feces than after intraperitoneal administration (40 versus 0.9%) (Bishara *et al.*, 1972). However, in connection with small repeated doses, the presence or kind of solvent made little difference; apparently the occurrence of bile in the intestine and the presence of some fat in the diet are sufficient to promote absorption of the compound.

Rothe *et al.* (1957) reported that after giving radioactive DDT by stomach tube as an emulsion of a peanut oil solution they were able to recover 41-57% of it in lymph drained from the animal by means of a cannula in the thoracic duct. Less than 0.1% of the activity was found in the urine, 7.4-37.1% was found in the feces or in the intestinal contents when the animals were killed, and 19-67% of the activity was found in the carcass. The total dose accounted for analytically varied

from 89 to 118%; thus, recovery was complete within the accuracy of the method. Of the administered DDT not found in feces and intestinal contents, 47-65% was found in the lymph. The animals that withstood the operation best had peak lymph flows of nearly 6 ml/hr. In these animals, DDT was absorbed at rates as high as 381 µg/hr; the highest rate of absorption was reached in 2-3 hr and was markedly reduced by the fourth hour after intubation. Fifty percent of the DDT-derived material found in the lymph was absorbed in the first 2.5-7 hr, and 95% was absorbed by 18 hr. Because the lymphatic duct in the rat is not a single vessel, Rothe *et al.* (1957) were unable to exclude the possibility that some or all of the DDT that they later recovered from the carcasses of their animals had been transported to the general circulation by collateral lymph vessels rather than by the hepatopancreatic system. They gave indirect evidence for supposing that little or no DDT is absorbed from the gastrointestinal system by the blood, and this has been confirmed by Palin *et al.* (1982). However, dieldrin is a similar compound, and only a small proportion of it administered as a peanut oil solution is absorbed by the lymph (Heath and Vandekar, 1964). The reason for the marked difference in the absorption of the two compounds is unknown.

Most of the DDT absorbed into the lymph is carried in the lipid core of chylomicrons and thence into the plasma proteins (Pocock and Vost, 1974; Sieber *et al.*, 1974). *p,p'*-DDT is taken up at a rate which is different from those of its metabolites and *o,p'*-DDT (Sieber, 1976) and which does not strictly parallel differences in lipid solubility.

As already stated, dermal absorption of DDT is very limited.

Distribution and Storage A detailed review of the literature (Hayes, 1959a) shows that a number of facts about the distribution and storage of DDT were established early either by single, classical papers now fully confirmed or by correlation of contributions from several laboratories. The major results may be summarized as follows.

1. DDT is stored in all tissues. Storage of the compound in blood, liver, kidney, heart, and the central nervous system was reported by Smith and Stohlman (1944).
2. Higher concentrations of DDT are usually found in adipose tissue than in other tissues (Ofner and Calvery, 1945).
3. Rats store DDT in their fat at all accurately measurable dietary levels, including the unintended residues in standard laboratory feeds.
4. Following repeated doses, storage in the fat increases rapidly at first and then more gradually until a peak or plateau is reached (Laug *et al.*, 1950). It was recognized that repeated doses at a moderate rate could result in greater total storage of DDT in the fat than a single dose at the highest rate that can be tolerated or even a single dose at a rate that frequently is fatal.
5. By plotting animal data published no later than 1950, it was possible to show that when other factors are kept constant the equilibrium storage of DDT in each tissue varies directly with the daily dosage (Fig. 2.13).
6. However (with the apparent exception of the dog), storage in the fat and perhaps in other tissues is less extensive in relation to dosage at higher dietary levels (Fig. 2.13).
7. The rat apparently tends to lose a part of the DDT it has stored in fat at the peak level reached in about 6 months, even though continued on the same diet (Laug *et al.*, 1950).
8. There is a measurable difference between the storage patterns of different species; that of the dog differs most (Fig. 2.13).
9. At higher dosage levels but not at ordinary residue levels the female rat consistently stores more DDT in its fat than the male when offered the same diet. The difference is accounted for only in part by the greater food intake of the female and must depend partly on more rapid biotransformation in the male. Other species show little or no sex difference.
10. The amount of DDT stored in the tissues is gradually reduced if exposure to the compound is discontinued or diminished.

It is interesting to note that even in the early studies there was satisfactory agreement between different authors and, in fact, between different laboratories. Later studies have amplified some of the findings.

More recent observations regarding storage include the finding that rats whose brains contain DDT at a concentration of 25 ppm or less (wet weight) usually survive, whereas higher levels tend to be fatal regardless of whether absorption followed one or many doses. The danger level is approximately the same in several species of birds (see Section 3.2.3.4). Of samples that may be collected from a living animal, the concentration of DDT in serum most accurately reflects its concentration in the brain, the critical tissue.

Adams *et al.* (1974) observed that about the same con-

centrations of DDT and related compounds are stored by male rats and by females that reproduce successfully. The lower storage in mated females probably is accounted for by transfer to the young via the placenta and the milk. However, other factors may be involved; no one really has accounted for the disposal of the increased DDT taken in by the female rat as a result of her high food intake during lactation.

When DDT, some of its analogs, and several other chlorinated hydrocarbon insecticides were fed to male and female rats for four generations, there was little variation in storage of the materials from one generation to another and no evidence of a continuing increase in succeeding generations (Adams *et al.*, 1974).

The concentrations of DDT in the blood and other tissues of the fetus are lower than those in corresponding tissues of the mother (Dedek and Schmidt, 1972).

The simultaneous administration of DDT and aldrin or of DDT and dieldrin may alter the storage of DDT or the other agent, or both. The effect varies from one species to another, as discussed in Section 15.2.2.3.

Studies of the distribution of DDT in various lipid fractions that are based on tissue extracts obtained with one or more organic solvents, like those of Kuz'minskaya *et al.* (1972a), are difficult to interpret because there is no way to determine how much of the material initially was associated with protein.

DDE constitutes about 4% of technical DDT. Most species convert some of the DDT they ingest to DDE. Finally, most species, including humans, store DDE more tenaciously than they do DDT, the greater part of which is metabolized by a different pathway from that of DDA and excreted more rapidly. The result is that DDE, expressed as a percentage of total DDT-related compounds, increases in individuals after DDT intake decreases and increases in successive steps of the food chain.

The Rhesus monkey apparently is an exception. Monkeys store DDE when it is fed to them. However, when feeding is stopped, the rate of loss of DDE stored in fat is more rapid than that of DDT (Durham *et al.*, 1963). Whether it is relative inability to form DDE, unusual ability to excrete it, or a combination of both that accounts for the fact that little or no DDE can be found in monkeys fed DDT is not entirely clear.

Metabolism The chemical nature of the chief metabolite excreted in the urine was first elucidated by White and Sweeney (1945). Rabbits were given DDT melting at 107–108°C at a rate of 100 mg/kg/day, 6 days/week, and their urine was collected. It contained a considerable amount of organic chloride, whereas normal rabbit urine did not. The authors isolated a crystalline material containing 25.36% chlorine and melting at 166–166.5°C, which was shown to be 2,2-bis(4-chlorophenyl)acetic acid (DDA). The product obtained from urine was identical to that synthesized from glyoxylic acid and chlorobenzene and with a compound obtained through the chemical degradation of DDT. Only 80–85% of the total organic chloride of the rabbit urine was found soluble in alkali and in bicarbonate. For this and other reasons, it was considered pos-

sible that DDA was not the only chlorinated organic compound present.

Later work by many authors has amply confirmed that DDA isomers are the major urinary metabolites of *p,p'*-DDT and *o,p'*-DDT in all mammals, including humans. It may be added that in spite of great strides in analytical chemistry, the nature of all excreted metabolites may not have been elucidated fully.

The ability of phenobarbital and especially diphenylhydantoin to promote the excretion of DDT was discovered in humans (Davies *et al.*, 1969) and later confirmed in animals (Cranmer, 1970; Alary *et al.*, 1971; Fries *et al.*, 1971).

The fact that DDE is stored in tissue was first demonstrated in connection with human fat (Pearce *et al.*, 1952; Mattson *et al.*, 1953). The authors did not know whether the compound resulted from partial degradation of DDT residues on plants or whether the DDE was formed during the process of digestion or after absorption. It is now known, using modern methods, that some of our food contains DDE but that humans are capable of forming the product from DDT.

That portion of the metabolism of DDT that leads to DDA in rats was explored by Peterson and Robinson (1964), who gave evidence for the sequence of changes leading to DDA involving reduction to 1,1-dichloro-2,2-bis(4-chlorophenyl)ethane (DDD) followed by dehydrochlorination to 1-chloro-2,2-bis(4-chlorophenyl)ethene (DDMU), which was apparently converted to 2,2-bis(4-chlorophenyl)ethanol (DDOH) via 2,2-bis(4-chlorophenyl)ethene (DDNU). The compound identified by Peterson and Robinson (1964) as a "probable" intermediate aldehyde between *p,p'*-DDOH and *p,p'*-DDA was later synthesized and shown to be highly labile (McKinney *et al.*, 1969), confirming the guess by Peterson and Robinson that it is unlikely to accumulate in tissues in measurable amounts. Kujawa *et al.* (1985) have obtained evidence for its formation from *p,p'*-DDD by rat liver homogenates and its presence in the urine of rats injected with DDD. Abou-Donia and Menzel (1968) identified two additional metabolites, bis(*p*-chlorophenyl)methane (DDM) and bis(*p*-chlorophenyl) methyl ketone (DBP) in chicken eggs and young chicks. Not only was DBP found to result from the metabolism of DDA with DDM as an intermediate, but DBP was the only metabolite of DDE administered directly to eggs or chicks.

Organ perfusion studies indicated that the liver is capable of biotransformation of DDT, DDE, DDD, DDMU, and other possible metabolites (Datta and Nelson, 1970). Cultures of human embryonic lung cells are capable of metabolizing DDT to DDA via DDD (North and Menzer, 1973).

When DDA was discovered, it was postulated on chemical grounds that DDE was a step in its formation (White and Sweeney, 1945); however, rats which produced both DDE and DDA from DDT were said by Peterson and Robinson (1964) to be incapable of forming DDA when fed preformed DDE. This finding was contradicted by Datta (1970) and by Datta and Nelson (1970), who claimed that ^{14}C -labeled *p,p'*-DDE was converted by rats to 1-chloro-2,2-bis(4-chlorophenyl)ethene (*p,p'*-DDMU), which then underwent further metabolism to *p,p'*-DDA. Datta suggested that the predominance of detoxi-

tion via DDE or DDD may depend on physiological response or the amount of toxicant used. The fact remains that DDE is stored more tenaciously than DDT.

The way in which DDE is lost from storage remained something of a mystery. In humans (Cueto and Biros, 1967), seals, and guillemots (Jansson *et al.*, 1975) part of it is excreted unchanged, but the fact that its elimination is promoted by induction of microsomal enzymes (see Use Experience in Section 15.3.1.3) strongly suggested that it undergoes metabolism, conjugation, or both. That metabolism does occur was first demonstrated by identification of two hydroxylated derivatives of DDE in the feces of wild seals and guillemots and in the bile of seals (Jansson *et al.*, 1975). When *p,p'*-DDE was fed to rats, the same metabolites and one other were isolated from the feces, and within the first 6 days they accounted for about 5% of the dose (Sundström *et al.*, 1975). Later, a fourth hydroxylated derivative was identified from the feces of rats fed *p,p'*-DDE. The compounds are *m*-hydroxy-*p,p'*-DDE [1,1-dichloro-2-(*p*-chloro-*m*-hydroxyphenyl)-2,2(*p*-chlorophenyl)ethylene, the major metabolite], *o*-hydroxy-*p,p'*-DDE, *p*-hydroxy-*m,p'*-DDE (the product of an NIH shift), and *p*-hydroxy-*p'*-DDE. A scheme involving *m,p*-epoxy-*p,p'*-DDE and *o,m'*-epoxy-*p,p'*-DDE was proposed for the formation of these metabolites as well as a fifth metabolite (Sundström, 1977). Neither the fifth metabolite nor the hypothetical intermediates have been isolated. In mice, feeding DDE increased the hepatic levels of radioactivity from $[^{14}\text{C}]$ DDE and decreased that in the urine and feces (Gold and Brunk, 1986). The only metabolite identified was the *o*-hydroxylated product.

DDE is metabolized not only to easily excretable phenols but also to *m*-methylsulfone-*p,p'*-DDE. In the blubber of seals from the Baltic, this compound was found in a concentration of 4 ppm along with DDE (138 ppm), DDD (10 ppm), DDT (78 ppm), and various polychlorinated biphenyls (PCBs) and their metabolites (150 ppm) (Jensen and Jansson, 1976). Sulfur-containing metabolites of halogenated aliphatic and aromatic chemicals usually arise by initial conjugation with glutathione. The possibility of glutathione-derived conjugates of DDT seems to be a virtually unexplored field.

Because DDT causes liver tumors, particularly in mice (See Table 15.7), some of the steps in its metabolism leading to reactive intermediates were studied with liver microsomal systems. The reductive dechlorination of *p,p*-DDT to DDD can occur with a cytochrome P-450 system, especially under anaerobic conditions (Hassall, 1971; Isaac and Matsumura, 1980; Zaidi, 1987). A one-electron reduction of DDT to the 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethyl radical seems to occur, followed by abstraction of a hydrogen atom, possibly from lipid, to give DDD (Kelner *et al.*, 1986). The reduction of DDT to DDD is stimulated by thiols in an unknown manner. The formation of an intermediate radical explains binding to microsomal lipid, especially under anaerobic conditions (Baker and Van Dyke, 1984). DDD, on the other hand, needs aerobic conditions for binding, implying that further metabolism is required. Other studies with mouse liver microsomes have shown the formation of 2,2-bis(*p*-chlorophenyl)-1,2-ethanediol

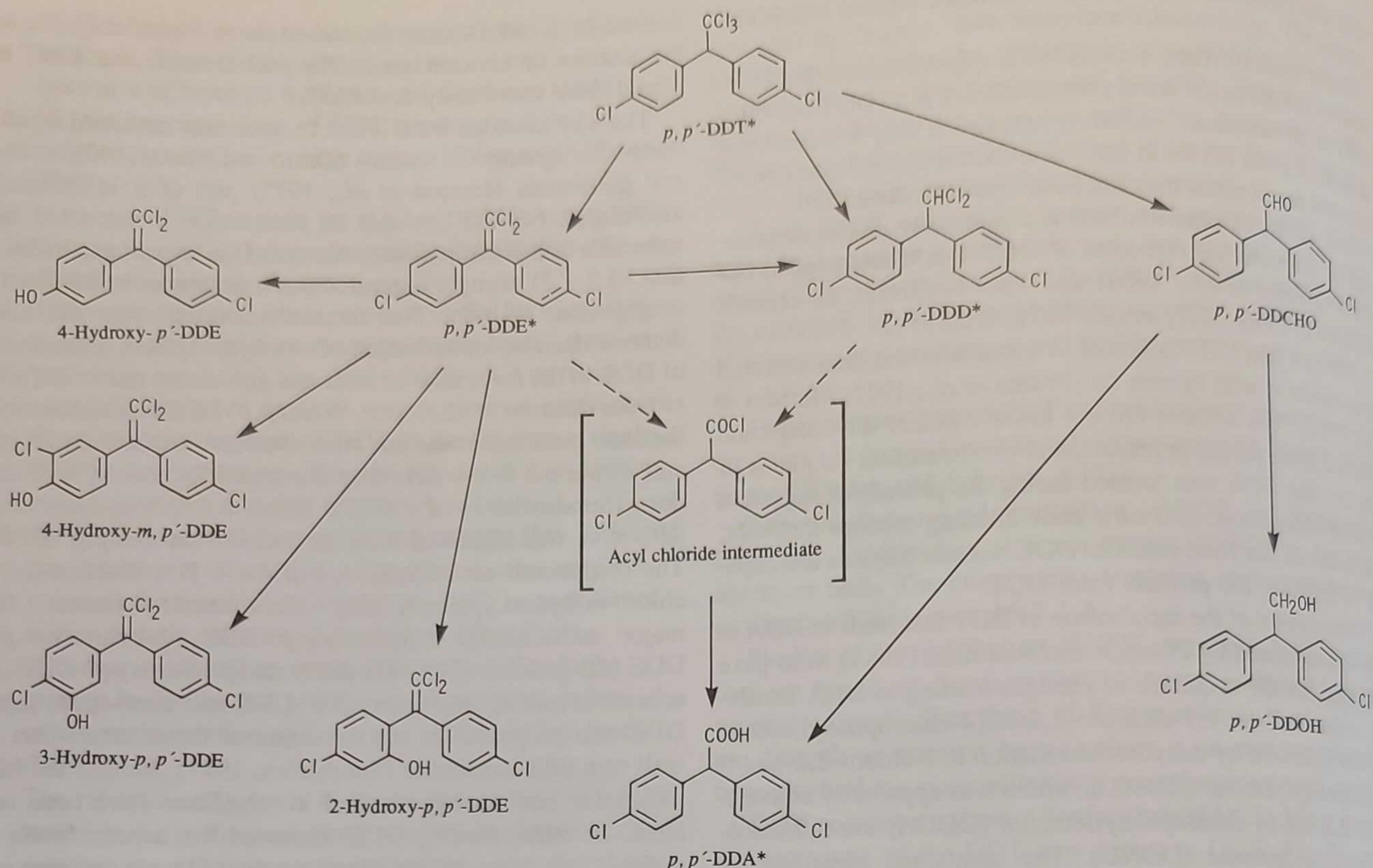


Figure 15.1 Metabolites of *p,p'*-DDT and the postulated route of metabolism in the rat. The metabolites indicated by an asterisk have been found in humans.

(DDNU-diol) from DDNU, suggesting that a reactive epoxide intermediate might be formed (Planche *et al.*, 1979). When synthesized, however, the ethylene oxide (DDNU-oxide) was not mutagenic.

In a series of papers, Gold and colleagues examined the metabolism of DDT metabolites in mice *in vivo*. The results seem to be a little different from that previously accepted for rats. It is thought that DDMU can undergo epoxidation; the resulting mutagenic epoxide is hydrolyzed and oxidized to 2-hydroxy-2,2-bis(4-chlorophenyl)acetic acid (α OH-DDA), which is excreted in the urine (Gold *et al.*, 1981; Gold and Brunk, 1982). Another route of metabolism of DDT in both the mouse and hamster (Gold and Brunk, 1982, 1983, 1984) seems to be the formation of DDA by a route involving hydroxylation on the C-1 side chain carbon of DDD (see Fig. 15.2). Loss of HCl gives an intermediate acyl chloride, 2,2-bis(4-chlorophenyl)acetyl chloride (Cl-DDA), capable of reacting with cellular proteins, DNA, etc. or losing water to give DDA.

Since this work, the metabolism of DDT in rats has been reexamined (Fawcett *et al.*, 1981, 1987) and seems to be similar to that described above for hamsters and mice. The conversion of *p,p'*-DDD to *p,p'*-DDA occurs primarily by hydroxylation leading to Cl-DDA, which on hydrolysis gives DDA. This acyl chloride may also be formed from DDE via an epoxidation route. Although DDMU is converted to DDA (Gold and

Brunk, 1984; Fawcett *et al.*, 1987), there is now considerable doubt as to whether it is an important intermediate in DDT metabolism. In addition, there is evidence to suggest that DDOH is a reduction product of DDCHO formed directly from DDT and not a precursor. A current scheme for the metabolism of *p,p'*-DDT in rats is shown in Fig. 15.1 and is still incomplete after nearly 40 years of study. However, it is possible that this will need to be amended. For instance, the role of DDOH still appears to be uncertain (Kujawa *et al.*, 1985).

The conversion of *o,p'*-DDT to *p,p'*-DDT has been reported (Klein *et al.*, 1965; French and Jefferies, 1969), but when the possibility was reinvestigated using ^{14}C -labeled *o,p'*-DDT, no conversion could be detected (Cranmer, 1972). The chromatographic peak closely resembling that of *p,p'*-DDT observed in the earlier studies undoubtedly is the result of a metabolite of *o,p'*-DDT.

The opposite conversion, namely biotransformation of *p,p'*-DDT or *p,p'*-DDD to the corresponding *o,p'*-compounds, has been reported in chicken egg and young chicks (Abou-Donia and Menzel, 1968) but has not been confirmed.

Compared to *p,p'*-DDT, the more rapid excretion of *o,p'*-DDT is explained at least in part by the observed ring hydroxylation of the parent compound in rats (Feil *et al.*, 1973) and chickens (Feil *et al.*, 1975) and of its metabolite *o,p'*-DDD in rats (Reif and Sinsheimer, 1975) and humans (Reif *et al.*, 1974).

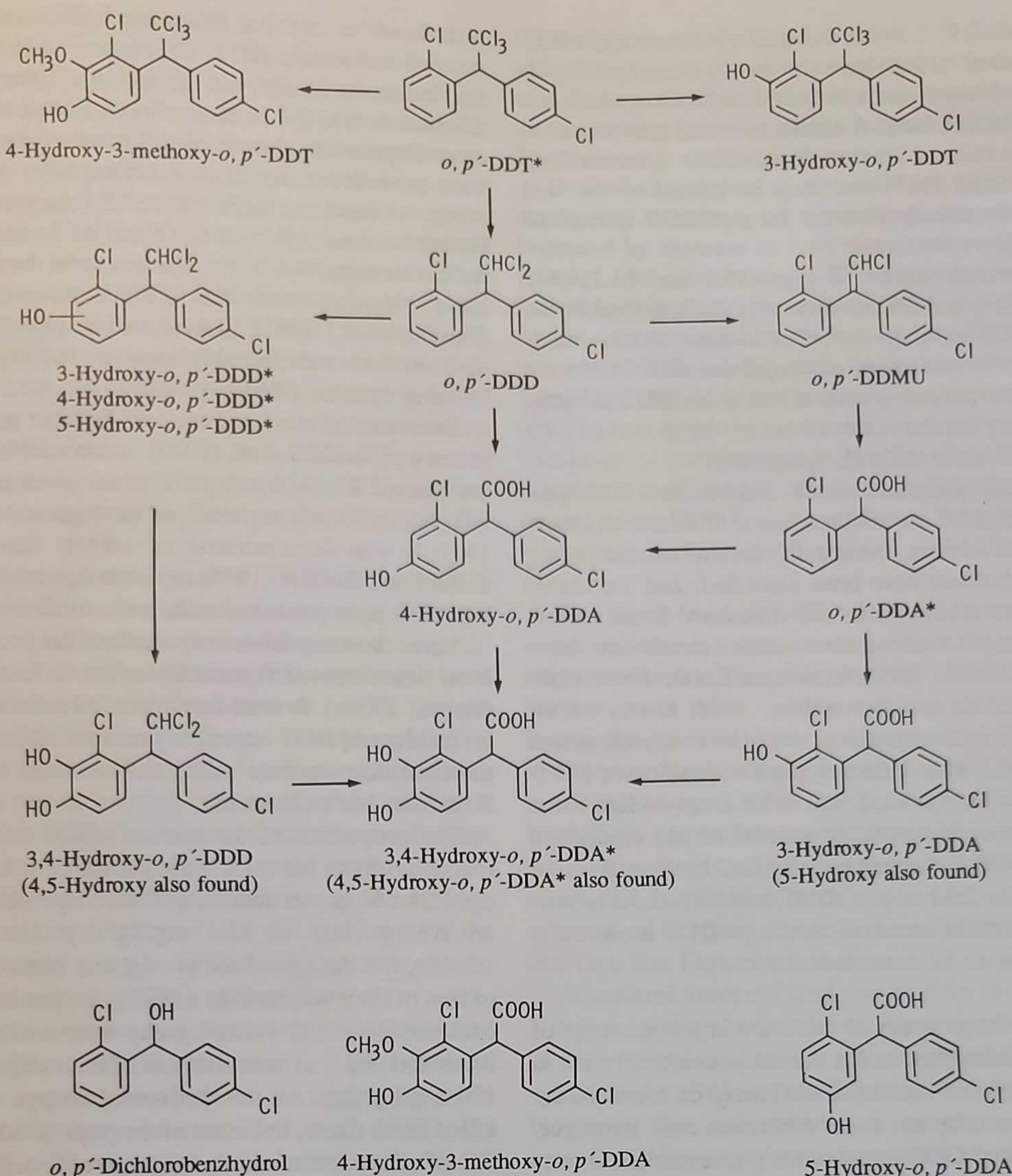


Figure 15.2 Metabolites of *o,p'*-DDT and the main derivative *o,p'*-DDD in rats. The sequence of metabolism shown may have to be evolved in light of recent investigations of *p,p'*-DDT metabolism. Compounds indicated by an asterisk have been found in humans, including those humans treated with large doses of *o,p'*-DDD. In rats, glycine and serine conjugates of *o,p'*-DDA have been found in the urine, and the aspartic acid conjugate of *o,p'*-DDA has been found in the feces.

(see Fig. 15.2). At least 13 metabolites were detected in rats and 15 in chickens. Ring hydroxylation, which has not been observed with *p,p'*-DDT or *p,p'*-DDD (but has been seen with *p,p'*-DDE), was present in all species. There were, however, some species differences. For example, *o,p'*-DDE and three hydroxylated *o,p'*-DDEs were found in the excreta of chickens but not in the excreta of rats. In two patients with adrenal carcinoma for which they were receiving *o,p'*-DDD at a rate of 2000 mg/day, as much as 46–56% of the daily intake was recovered in the urine following acid hydrolysis. Just over half of the recovered material was in the form of *o,p'*-DDA, but the remainder was in the form of hydroxylated derivatives, specifically *m*-hydroxy-, *p*-hydroxy-, *m*-hydroxy-*p*-methoxy-, and *p*-

hydroxy-*m*-methoxy-*o,p'*-DDA. Some other hydroxylated compounds were found in trace amounts. All hydroxylation had occurred on the ring that had its chlorine in the *o* position (Reif *et al.*, 1974). When the metabolism of a single 100-mg oral dose of *o,p'*-[¹⁴C]DDD was studied in rats, averages of 7.1 and 87.8% of the activity were recovered in the urine and feces, respectively, within 8 days (Reif and Sinsheimer, 1975). The high recovery indicated rapid excretion with little storage.

o,p-DDD is specifically toxic for the adrenal cortex in a number of species including humans. *In vitro* studies suggest that this is due to its activation in adrenal mitochondria to a metabolite which binds covalently. Unlike the situation in liver, a metabolite more polar than DDA is also produced

(Martz and Straw, 1977, 1980; Pohland and Counsell, 1985). Recently, Lund *et al.* (1988) have shown that 3-methysulfonyl-*o,p*-DDE is selectively covalently bound and toxic to the adrenal zona fasciculata of mice. A similar situation may prevail to account for the covalent binding of *o,p*-DDD in mouse lung (Lund *et al.*, 1986, 1989) and may be related to the acyl chloride formation already reported for *p,p'*-DDT in rats and mice (Fig. 15.1).

Of the compounds shown in Figs. 15.1 and 15.2, only DDT, DDD, DDE, and DDA commonly are reported in the tissues or excreta of animals, including humans. A novel finding has been the identification of conjugates of DDOH with fatty acids in the livers and spleens of rats given DDT (Leighty *et al.*, 1980). They can be removed *in vivo* by treatment with bile salts, heparin, or lecithin (Leighty, 1981).

Although microorganisms, plants, insects, and birds produce many of the same metabolites found in mammals, there are interesting differences. Nearly 20 derivatives (including mammalian metabolites) have been identified, and the chemical structures of several more are still unknown. Some aspects of nonmammalian, as well as mammalian, metabolism have been reviewed (Menzie, 1969; Klein and Korte, 1970; Fishbein, 1974; Schroeder and Dorozalska, 1975; Korte, 1979). The metabolism of microorganisms and plants, as well as that of domestic animals, may influence the composition of DDT-derived residues in human food, but there is no evidence that these residues contain a significant amount of any compound not formed from DDT by human metabolism. In view of recent developments in the field of *p,p'*-DDT metabolism, it is possible that in the future the metabolism of *o,p'*-DDT as shown in Fig. 15.2 may have to be amended.

Excretion When large doses of DDT are ingested, some of the compound is unabsorbed and is passed in unaltered state in the feces. Only traces of unaltered DDT may be found in the feces when exposure is by any route other than oral. However, true fecal excretion of DDT metabolites was established irrespective of the route of administration (Hayes, 1965). In humans the ratio is obviously different. Although the excretion of DDT-related material in the feces of humans receiving 35 mg/person/day has been studied using colorimetry (Hayes *et al.*, 1956), this result has never been confirmed by gas chromatography, even in connection with workers whose exposure was heavy and prolonged (Hayes, 1982). Either DDT metabolites are not excreted by humans in the feces to any important degree, or they are excreted in one or more forms different from those already demonstrated in rats.

The bile appears to be the principal source of DDT metabolites in the feces of rats. When the bile duct was cannulated before intravenous injection of radioactive DDT, 65% of the dose was recovered in the bile, 2% in the urine, and only 0.3% in the feces (Jensen *et al.*, 1957), and the possibility of some contamination of the feces by urine could not be excluded.

The different routes of excretion are not unrelated. Burns *et al.* (1957) found that there was an increase in urinary excretion

of radioactive material following ligation of the bile duct in rats fed radioactive DDT. This is an indirect confirmation in the finding by Jensen and his colleagues that most of the metabolites in bile are DDA or closely related to it. Although an enterohepatic circulation of the metabolites of DDT has not been proved directly, it seems likely that such a circulation exists, as has been demonstrated for ethylan. The difference between the excretion of DDT and its metabolites in rats and the slower excretion in birds seems to be the reduced ability of birds to further metabolize DDE and convert DDD to DDA (Fawcett *et al.*, 1981). The excretion of DDE in rats is dependent on dose and probably involves induction of drug-metabolizing systems (Ando, 1982).

Demonstration of excretion of DDT in milk was first published by Woodard *et al.* (1945) in connection with a dog fed at the rate of 80 mg/kg/day. Within a short time, excretion of DDT in milk was reported in rats, goats, and cows, and in 1951 it was demonstrated in women (Lang *et al.*, 1951). Telford and Guthrie (1945) reported that rats fed a diet containing 1000 ppm produced milk toxic to their young.

Since the early laboratory studies, the presence of DDT has been demonstrated repeatedly in the milk of cows. A review (Hayes, 1959a) showed that cows fed substantial, but nontoxic, residues of DDT commonly excrete 10% or slightly more of the total dose in their milk, and amounts slightly more than 30% have been observed.

The proportion of the mother's DDT intake that could be recovered from her milk varied from 12.6 to 30.2% and averaged 24.6% in rats receiving the compound from their diet at an average rate of 32.4 mg/kg/day. Under these circumstances, the dosage of the young was somewhat less than half of that of their mothers on a milligram per kilogram basis. The oral dosage of 32.4 mg/kg/day was well tolerated by both dams and pups, as was also true of an intraperitoneal dosage of 100 mg/kg/day. An intraperitoneal dosage of 200 mg/kg/day killed some dams, but most of the pups of other dams survived. All of the pups of these mothers experienced reduced milk intake and reduced weight gain. The concentration of DDT in the brains of these pups was much lower than in pups killed by oral administration of the compound, indicating that the young of mothers receiving massive dosages of DDT suffer malnutrition but not poisoning (Hayes, 1976b).

Wilson *et al.* (1946) showed that DDT was secreted from the skin of a cow maintained on an oral dosage of about 53 mg/kg/day.

Because DDA is the main form in which DDT is excreted, it might be expected that, following its direct administration, DDA would be excreted relatively efficiently, and this is true. It was found very early that, during the first several days after oral dosing, rabbits excreted DDA in the urine approximately 15 times faster than animals given DDT at an equivalent dosage. Although the rate of DDA excretion increased somewhat, the rate of excretion associated with DDT increased more rapidly, so that the values differed by a factor of only 5 after day 20 of feeding (Smith *et al.*, 1946).

Biochemical Effects There is reason to think that the mechanism of action of DDT is its effect on membranes in the nervous system, especially axonal membranes. Certainly, action on membranes is a fundamental property of the compound. Its action on conductance in an inanimate membrane and in the membranes of the giant axons of cockroaches and lobsters is discussed in Section 4.1.2.3. The effect on axons may be related to inhibition of Na^+ -, K^+ -, and Mg^{2+} -adenosine triphosphatase derived from a nerve ending fraction of rabbit brain that is inhibited by DDT and is discussed in the same section. A similar enzyme that binds [^{14}C]DDT has been isolated from the synapses of rat brain (Bratowski and Matsumura, 1972). There has been considerable interest in a Ca-ATPase which may regulate calcium levels at the axon surface (Ghiasuddin and Matsumura, 1979), and DDT is known to cause prolonged opening of the ion gates of the sodium channel perhaps by affecting phosphorylation in the α -subunit protein (Ishikawa *et al.*, 1989).

At a supralethal dosage of 600 mg/kg, DDT caused in rats a marked decrease in the concentration of cortical and striatal acetylcholine and of brain stem norepinephrine and a significant increase in brain stem 3-methoxy-6-hydroxyphenylglycol and 5-hydroxyindoleacetic acid (Hrdina *et al.*, 1973; Hudson *et al.*, 1985; Tilson *et al.*, 1986). *p*-Chlorophenylalanine blocked all of the neurotoxic signs of poisoning, and other inhibitors blocked one or another but not all of the effects. It was concluded that changes in the metabolism of 5-hydroxytryptamine and norepinephrine may be responsible for DDT-induced hypothermia and acetylcholine may be related to tremors and convulsions (Hrdina *et al.*, 1973). However, the situation is complex and many factors are involved (Herr *et al.*, 1985, 1986; Hudson *et al.*, 1985). Although spinal α -adrenoceptors have been proposed as modulating DDT-induced tremor (Herr and Tilson, 1987) attenuation of DDT-induced motor dysfunction requires blockade of α , adrenoceptors in region other than solely the spinal cord (Herr *et al.*, 1989). At a lower dose of DDT (180 mg/kg), but one which still induced convulsive tremor, acetylcholine and cyclic GMP were increased in the cerebellum (Aldridge *et al.*, 1978). In adult rats and mice there is a decrease in the cholinergic muscarinic receptors of rat brain (Eriksson *et al.*, 1984), particularly in the cerebellum (Fonseca *et al.*, 1986). A particularly interesting finding is that the palmitic acid conjugate of DDOH can also have this effect (Eriksson and Nordberg, 1986). Disturbances of brain lipid metabolism have been observed in monkeys after chronic exposure to DDT (Sanyal *et al.*, 1986). Khaikina and Shilina (1971) reported that administration of DDT to rats at only one-fifth of the LD 50 for 20 days increased by 188% the amount of 5-hydroxyindoleacetic acid excreted in their urine. This indicated a change in the metabolism of serotonin, but probably does not support a serotonin deficiency as a DDT mode of action (Chung Hwang and Van Woert, 1981).

It is evident that many of the side effects of DDT are the result of its induction of microsomal enzymes. Both the dosage response and the morphological aspects and implications of

this induction are discussed in Section 15.2.3.2. Background information on the biochemical aspects of induction of microsomal enzymes by DDT and other pesticides has been reviewed earlier (see Sections 3.1.2 and 3.1.3 and Table 3.6). The following additional observations are of interest.

Oral administration of *o,p'*-DDT to dogs at a rate of 50 mg/kg/day stimulates the microsomal enzymes of the liver as indicated by increase in liver size, total protein, microsomal protein, and cytochrome P-450 concentration and by direct measurements of enzyme activity. These changes in the liver are initially accompanied by an increase in the size of the adrenals and of the cells of the zona fasciculata; these cells become vacuolated and devoid of acidophilic cytoplasm, and their nuclei become hyperchromatic and often peripheral in position. Synthesis of corticosteroids by the adrenal is not blocked (Copeland and Cranmer, 1974). Thus, the effect of a substantial dosage of *o,p'*-DDT is quite different from that of *o,p'*-DDD, although part of the metabolism of *o,p'*-DDT must be by that route.

The tissue level of DDE necessary to induce liver microsomal enzymes is lower in the rat than in the quail (and presumably other birds). Thus Bunyan *et al.* (1972), using residues in the heart as an index, found a maximal increase in cytochrome P-450 per gram of liver and a maximal activity of aniline hydroxylase levels at tissue levels of approximately 3 ppm DDE in rats and 40 ppm DDE in quail. However, at any given dietary level, higher tissue levels were reached by quail than by rats, so the dosage responses of the two were similar. These authors concluded that DDE is more important than DDT in inducing microsomal enzymes, but in humans the opposite appears to be true (see Use Experience in Section 15.3.1.3).

In squirrel monkeys (and presumably in other species) only 2 days on a vitamin C-deficient diet impairs both the induction of *O*-demethylase and the stimulation of the glucuronic acid system by DDT (5 mg/monkey/day) (Chadwick *et al.*, 1971b). In guinea pigs, maintenance of induction of microsomal enzymes requires a higher dietary level of vitamin C than does prevention of scurvy (Wagstaff and Street, 1971a).

The association of lipids with the function of microsomal enzymes is recognized generally, as is the fact that DDT induces these enzymes. Therefore, it might have been expected that DDT and essential fatty acids would interact. Tinsley and Lowry (1972) found that the growth of female rats receiving *p,p'*-DDT at a dietary level of 150 ppm was depressed if they received a diet deficient in essential fatty acids but was slightly stimulated if they received the same diet supplemented with these acids. Another parameter influenced by the same variables was the ratio of various liver lipids. The changes in fatty acid composition were related to the proliferation of hepatic smooth endoplasmic reticulum; it was suggested that DDT influenced essential fatty acid metabolism by increasing the demand for them. Sampson *et al.* (1980) found that DDT did not exacerbate aspects of essential fatty acid deficiency but did alter lipid metabolism in an unexplained way.

In contrast, a variety of diets (containing fats that may occur

in the human diet and that were in approximately the same proportion as fats in typical human food in the United States had little or no influence on the storage of DDT and a wide range of pesticides fed to rats for four generations in combination at rates only 200 times those found in the Market Basket Study of food in the United States (Adams *et al.*, 1974). Fat mobilization can cause rapid release of stored DDT, but this does not seem to be associated with any major toxic effect assessed pathologically or biochemically (Mitjavila *et al.*, 1981b).

DDT has been shown *in vitro* and sometimes *in vivo* to influence some enzymes of intermediary metabolism and other miscellaneous enzymes. For instance, DDT and a variety of analogs have been shown to affect isolated rat liver mitochondria but the significance of this *in vivo* is uncertain (Ohyama *et al.*, 1982). So far evidence is lacking that the degree of this inhibition in the intact organism is sufficient to have any influence on function.

The hyperglycemia observed during much of the early part of acute poisoning may be associated with an increase in four gluconeogenic enzymes (pyruvate carboxylase, phosphoenol-pyruvate carboxykinase, fructose-1,6-diphosphatase, and glucose-6-phosphatase). Increase in these enzymes in the renal cortex of rats has been observed after a single dose at a rate as low as 100 mg/kg or greater or following 45 daily doses at rates of 5 or 25 mg/kg/day. The changes are not mediated through release of corticosteroids from the adrenal glands (Kacew and Singhal, 1973). The fact that 100 mg/kg is the smallest single dosage that produced a statistically significant change in these enzymes indicates that their alteration is a complication rather than a cause of poisoning.

A review (Hayes, 1959a) of early literature indicates that high concentrations of DDT inhibit phosphatidase, muscle phosphatases, carbon anhydrase, and oxaloacetic carboxylase and increase the activity of cytochrome oxidase and succinic dehydrogenase. However, none of these changes with the possible exception of inhibition of carbonic anhydrase could be shown to have any connection with the toxic action of DDT or even with its side effects. Neal *et al.* (1944) reported a small but consistent increase in the volume of urine excreted in 24 hr when dogs were dosed orally or by insufflation at the rate of 100 mg/kg/day. No other change in the urine and no change in kidney function was demonstrated. The possibility that increased urinary output is related to the inhibition of carbonic anhydrase (Torda and Wolff, 1949) may deserve attention. However, reexamination of data from volunteers receiving 3.5 or 35 mg/person/day indicated no increase in urinary volume compared with controls (Hayes *et al.*, 1971).

On the other hand, many enzymes including plasma amylase, aldylase, glutamic-pyruvic transaminase, and isocitric dehydrogenase were not changed in squirrel monkeys given dosages from 0.05 to 50 mg/kg/day, the latter of which proved fatal within 14 weeks (Cranmer *et al.*, 1972).

Effects on the Nervous System The major toxic action of DDT is clearly on the nervous system, probably by slowing

down closing of "gates" in axon sodium channels (Dubois and Bergman, 1977; Woolley, 1982, 1985; Hong *et al.*, 1986), and it requires an intact organism for full expression. The fact that DDT causes a myotonic response in muscle and substitution of a train of spikes for the normal diphasic electroneurogram (Eyzaguirre and Lilienthal, 1949) is in marked contrast to the absence of detectable injury or, in fact, any response in other isolated tissues. As early as 1945, Lewis and Richards found DDT to be inert when it was exposed to tissue cultures of heart, kidney, stomach and intestine, liver, and muscle from 7- to 9-day chick embryos and of brain and spleen from a 1-day rat. The physiology of the cells including the mitoses of fibroblasts was normal. The migration and extension of the various cells were unchanged. The authors stated that "living fibrilloblasts, as they moved about in the cultures, sometimes touched or even migrated over DDT crystals without appreciable injury to themselves during a period of several days." Some observations were carried out for periods as great as 21 days.

In spite of the importance of the nervous system, a detailed review of early literature indicates that although the presence of some specialized nervous function may be necessary for the manifestation of DDT poisoning, the mere occurrence of specialized nervous fibers in certain protozoa or the occurrence of a rather complex nervous system in mollusks is not sufficient to render these forms susceptible. Just as there is no explanation for the effect of DDT in susceptible species, so there is no explanation for the fact that certain species and even entire phyla are inherently resistant to the compound.

A review (Hayes, 1959a) of literature on the effects of DDT on the nervous system reveals that all major parts, both central and peripheral, are affected. Whereas effects on specific portions, notably the cerebellum and the motor cortex, have been viewed as of greatest importance, it probably is more accurate to emphasize the interaction of functions, all modified to some degree.

One sensitive measure of brain activity is the electrocorticogram. Farkas *et al.* (1968) found that the wave frequency showed considerable increase in resting rats that had received 20 mg/kg/day as a result of dietary intake. Rats that had received 5 mg/kg/day did not exhibit this change while at rest, but even these exhibited abnormalities when exposed to a rhythmic light stimulus. Electrical activity may become abnormal only a minute or two after administration of a large dose of DDT; four stages culminating in generalized seizures have been described by Joy (1973). Phenobarbital, but not diphenylhydantoin or trimethadione, was effective in stopping seizures.

The most characteristic effect of DDT in contrast to dieldrin, for example, is the production of tremor. Sufficient dosages of DDT produce tremor even at ambient temperatures that approach body heat. However, dosages of DDT that produce no other clinical effect make rats more sensitive to low temperatures, and this sensitivity may be demonstrated conveniently by having the rats swim to exhaustion in cool water. The ability of a rat to keep afloat is more dependent on coordination than on physical strength.

It was found that normal rats can swim for over 100 min in water 25°C or warmer but for only about 30 min at 23°C and less than 10 min at 15°C. At any given temperature, male rats could swim longer than females. Of the temperatures studied, the effect of DDT was most striking at 25°C; normal females swam for 117 min, whereas those that had received a dietary level of 50 ppm (2.62 mg/kg/day) swam only an average of 7 min. At 27°C, both groups of rats swam over 120 min, and at 37°C the swimming time of rats on a dietary level of 200 ppm approached or equaled that of normal animals. In order to expedite testing, the conditions were standardized at a water temperature of 19.9–20.2°C, and 0.006% sodium lauryl sulfate was added to the water to reduce the trapping of air in the fur, which tends to buoy up rats and permit them to swim longer. Under these conditions, the swimming time of normal animals averaged about 12 min when they were first tested but approached 16 min within a month if the animals were tested repeatedly. If DDT was fed for 2 weeks starting after the rats had become accustomed to swimming, those at a dietary level of 20 ppm showed a reduction in swimming time that was of questionable statistical significance. Those at a dietary level of 50 ppm showed a gradual decrease in swimming time during the 2-week exposure period and failed to return to the endurance of the controls in over a month after dosing was stopped. At dietary levels of 150 and 400 ppm, there was a sharp reduction in swimming time (to 7.3 and 4.0 min, respectively) on the first day of dosing, followed by a gradual decline during the remaining 13 days of dosing and then a slow, incomplete return toward normal (Hayes, 1982).

When measured by the same device 4 min after rats had swum to exhaustion, the tremor of a rat on a dietary level of 200 ppm involved much more energy than that of a normal rat, but the frequencies of the tremors were essentially identical—13–15/sec. In spite of the difference in energy, it appears likely that the tremorigenic action of DDT involves toxicity to that portion of the brain responsible for the control of ordinary shivering. In any event, the presence of tremor depends largely on the temperature of the head. This was demonstrated by Dr. Carl Rothe by placing a rat's head through a hole in a rubber sheet so that the rubber fit snugly about the neck and then varying the temperature of the head and the body relatively independently by separate sprays of either warm or cold water in front of and behind the sheet.

Like tremor, the coldness of the skin and ruffling of the fur seen in acute poisoning probably represent an indication of disturbed thermal regulation. Apparently, it was not until the work of Hrdina *et al.* (1975) that an increase of almost 3°C in body temperature was reported in rats following a fatal (600 mg/kg) oral dosage of DDT.

The central nervous systems of mice and hamsters are equally sensitive, the concentration of DDT in their brains at death being similar. However, after an oral dosage of 500 mg/kg, the DDT concentration of the mouse brain was twice that of the hamster. This cannot be explained by a difference in absorption, metabolism, or excretion but apparently is due to a difference in permeability of the blood–brain barriers of the two species.

When animals received DDT at a dietary level of 205 ppm for 6 weeks, the residues in fat and liver were seven to eight times higher in the mouse, a fact only partially explained by the greater food intake of mice relative to body weight. Although urinary excretion of [¹⁴C]DDT was similar in previously unexposed hamsters and mice, this excretion was stimulated in the hamster but little affected in the mouse by previous dietary exposure to DDT (Gingell and Wallcave, 1974).

Mice also differ from rats in their hormonal regulation of the basic activity of hepatic microsomal mixed-function enzymes as well as in the response of these enzymes to inducers (Chhabra and Fouts, 1974).

Cause of Death Death from DDT poisoning is usually the result of respiratory arrest. The heart continues to beat to the end and in some instances continues a little while after respiration stops. Deichmann *et al.* (1950) found that the onset of hyperirritability was accompanied by an increase in the frequency and amplitude of respiration. Later, with the occurrence of tremors, the depth of respiration frequently returned to a more normal level, but the rate remained high. In some animals respiration stopped suddenly after a deep inspiration during a tonic convulsion. In other animals the rate and amplitude decreased progressively and finally ceased without any terminal spasm. Animals that die of respiratory failure caused by DDT do so after a relatively long period of muscular activity that leaves them exhausted.

It was shown by Philips and Gilman (1946) and Philips *et al.* (1946) that the hearts of dogs given large intravenous doses of DDT were sensitized to epinephrine. This was true not only of injected epinephrine but also of the compound released by the adrenal glands during a seizure. Stimulated in this way, the sensitized hearts of dogs developed an irreversible, fatal ventricular fibrillation. However, the hearts of monkeys were able to recover from fibrillation and resume normal rhythm. It is not clear how important sensitization of the myocardium is when DDT is administered by other routes, but ventricular fibrillation may be the cause of death in animals that die suddenly soon after onset of poisoning.

Thus, DDT not only sensitizes the myocardium in a way similar to that of halogenated hydrocarbon solvents but also, through its action on the central nervous system, produces the stimulus that increases the likelihood of fibrillation.

There is no evidence that repeated, tolerated doses of DDT sensitize the heart. Rats were fed DDT at a dietary level of 200 ppm (about 10 mg/kg/day) for 8 months, during which they received weekly intraperitoneal doses of vasopressin, a compound which causes a temporary myocardial ischemia. Electrocardiograms showed no significant increase in cardiac arrhythmias in the DDT-fed rats compared with controls. Intravenous noradrenaline given at the end of the 8-month period did not produce a greater incidence of arrhythmias in the DDT-fed rats. The same results were obtained in rabbits treated in essentially the same way (Jeyaratnam and Forshaw, 1974).

Mutation and Carcinogenesis DDT has been tested in a number of ways for possible mutational effect. Much of this

work has been reviewed in detail together with most of the carcinogenicity studies shown in Table 15.7 (Coulston, 1985). For example, Shirasu *et al.* (1976) listed DDT as a negative chemical in microbial mutagenicity screening studies on 166 pesticides. The test system consisted of rec-assay utilizing H 17 Rec⁺ and M 45 Rec⁻ strains of *Bacillus subtilis* and reversion assays without metabolic activation using auxotrophic strains of *Escherichia coli* (WP 2) and *Salmonella typhimurium* (Ames series). The further studies with metabolic activation failed to reveal mutagenicity of DDT (Shirasu *et al.*, 1977). McCann *et al.* (1975) and McCann and Ames (1976) reported negative results on DDE in *S. typhimurium* testing with metabolic activation.

At a dosage of 105 mg/kg it produced no increase of dominant lethals in mice (Epstein and Shafner, 1968). However, concentrations of 10 ppm or greater produced chromosome breaks and exchange figures in a marsupial somatic cell line (Palmer *et al.*, 1972). Saturated solutions produced chromosome breaks in the root tips of onion and other plants (Vaarama, 1947). A slight mutagenic effect in mammals has been reported by Markarian (1966). Deletions plus gaps were reported to be more common in the chromosomes of mice that had received DDT. On the whole, *in vitro* tests of the mutagenicity of DDT have given only negative or dubious results (Coulston, 1985).

An unconventional test for mutagenicity involved examination of explants of pulmonary tissue from embryonic mice whose dams had been fed dietary concentrations of 10 and 50 ppm DDT. An increase of diffuse hyperplasia and focal proliferation was observed, but a dosage-response relationship was not clear. Some of the embryos were allowed to live and the experiment was repeated in subsequent generations. There was no continuing progression of the reported changes in succeeding generations (Shabad *et al.*, 1972).

DDT causes inhibition of intercellular communication in cultured rat liver cells (Williams *et al.*, 1981) and in hamster lung fibroblasts (Wärngård *et al.*, 1985, 1987, 1988) like other chlorinated chemicals. The exact significance of the effect is unknown, but it does not seem to involve direct activation of protein kinase C, unlike 12-*o*-tetradecanoylphorbol-13-acetate (Wärngård *et al.*, 1989). *o,p'*-DDT supports the growth of an estrogen-responsive tumor (Robison *et al.*, 1985a).

The question of whether DDT is carcinogenic really seems to be restricted to its action in the liver of some rodents. This matter and its relation to the induction of liver microsomal enzymes by DDT, by other chlorinated hydrocarbon insecticide, and by phenobarbital is discussed in Section 15.2.3.2. Some of the positive findings shown in Table 15.7 have not been found in other studies [National Cancer Institute (NCI), 1978a]. However, there is still the evidence that DDT can act as a promoter of carcinogenesis initiated by aflatoxin and of other chemicals *in vitro* and *in vivo* (Peraino *et al.*, 1975; Schulte-Hermann, 1985; Rojanapo *et al.*, 1987).

Other Miscellaneous Effects on Organs and Tissues The effects of DDT and other chlorinated hydrocarbon insecticides on the liver are discussed in Section 15.2.3.2.

Many early reports reviewed by Hayes (1959a) indicate that large doses of DDT may have no effect on the blood or they may produce a moderate leukocytosis and a decrease in hemoglobin, with or without a decrease in the concentration of red cells. The leukocytosis probably is secondary to stimulation of the sympathetic nervous system, while the loss of hemoglobin may be nutritional in origin. Later study has not confirmed the early results. A range of hematologic parameters remained unchanged in squirrel monkeys dosed orally at rates of 0, 0.05, 0.5, 5, and 50 mg/kg/day, even though the highest dosage was fatal within 14 weeks (Cranmer *et al.*, 1972).

Average protein-bound iodine (PBI) levels of 5.42 and 6.93 µg/%, respectively, were reported in the sera of 42 workers occupationally exposed to chlorinated hydrocarbon insecticides and 51 workers not so exposed. The difference was statistically significant even though all values fell within the normal range of 4–8 µg/% (Wassermann *et al.*, 1971). It was not recorded whether the workers involved were from the same factory as those with 10 or more years of occupational exposure whose plasma DDT levels were reported by M. Wassermann *et al.* (1970a). The small difference in PBI levels is difficult to evaluate. Goldman (1981) has reported that after a single large dose (100 mg/kg) to rats thyroidal ¹³¹I release was completely inhibited for more than 12 hr. It was the view of Clifford and Weil (1972) that there was no evidence that occupational exposure to DDT has had any effect on human endocrine organs.

The possibility that some pesticides, including DDT, are probiotic has been discussed in Section 2.4.14. Although this general question remains open, one group of investigators has shown clearly that what at first appeared to be an immunological response really involved a quite different, predictable effect. Briefly, it was shown that guinea pigs sensitized to diphtheria toxoid were less susceptible to anaphylaxis in response to a challenge dose of the toxoid if they were pretreated with DDT at a dosage of only 10–20 mg/kg/day. Direct measurement of antitoxin production indicated little or no difference between protected and unprotected animals. Furthermore, some protection was given by DDT administered for only 3 days prior to the induction of anaphylaxis (Gabliks *et al.*, 1973, 1975). Further study showed that DDT treatment reduced the histamine levels in the lungs of both immunized and nonimmunized animals. The number of detectable mast cells was also reduced; this was true whether the count was made in tissues from guinea pigs dosed systemically with DDT or in lungs and mesenteries from untreated animals exposed to DDT *in vitro* at concentrations ranging from 10 to 45 ppm. These results indicated that the protection offered by DDT was the result of a reduction of the amount of histamine available for sudden release in response to a challenge dose of toxoid (Askari and Gabliks, 1973). Regardless of exposure to DDT, immunization leads to an increase in detectable mast cells (Gabliks *et al.*, 1975). DDT has been reported to cause acute renal failure in rats after intravenous infusion (Koschier *et al.*, 1980).

Effects on Reproduction It was shown very early (Burlington and Linderman, 1950) that DDT produces a striking inhibition of testicular growth and secondary sexual charac-

teristics of cockerels when injected subcutaneously in dosages as high as 300 mg/kg/day. Changes in the testis involve the tubules and not the interstitial tissues, and they have been attributed to an estrogen-like action of DDT.

It must be noted that the action of DDT on the testis of chickens is dosage related. Before the problem of residues became evident, DDT was used extensively for control of lice and common mites on chickens without any adverse effects on egg production or other aspects of reproduction. Many rats would be killed the first day if they were given the dosage of DDT that has been shown to affect the testis of cockerels. The report that under special conditions DDT has a gonadotoxic effect (Rybakova, 1968) is of questionable significance in view of the results of multigeneration tests in rats, mice, and dogs. Dean *et al.* (1980) were unable to demonstrate any changes in either serum androgens or testicular synthesis of testosterone in young rats after exposure to DDT despite significant induction of metabolism of testosterone by isolated hepatic microsomes.

Intraperitoneal injection of as little as 5 mg/kg of technical DDT or 1 mg/kg of *o,p'*-DDT causes a significant increase in weight of the uterus of normal immature female rats or of ovariectomized adult females. A much smaller stimulation is caused by *p,p'*-DDT. Treatment of rats with DDT, especially *o,p'*-DDT, 2 hr before injection of [6,7-³H] estradiol-17 inhibited uptake of the hormone by the uterus *in vivo*, possibly by competition for binding sites. Isomers of DDD and DDE do not influence uterine weight or the binding of estradiol (Welch *et al.*, 1969). It seems unlikely that metabolic activation of *o,p'*-DDT is necessary as is true of *o,p'*-methoxychlor (Kupfer and Bulger, 1979). The action of *o,p'*-DDT on the uterus seems to be as a long-acting agonistic estrogen interacting with the same receptor as 17 β -estradiol and causing the formation of the so-called induced protein (Ireland *et al.*, 1980; Robison *et al.*, 1984; Galand *et al.*, 1987). However, some differences from estradiol have been recorded (Robison *et al.*, 1985b). The lesser enantiomer of *o,p'*-DDT seems to be the active isomer (McBlain, 1987). The binding and estrogenic activity of DDT analogs in rats is only about 1/10,000 as great as that of diethylstilbestrol (Nelson, 1973).

A considerably smaller dosage of *o,p'*-DDT resulting from a dietary level of 10 ppm for 2–9 months had no effect on reproduction in ewes (Wrenn *et al.*, 1971b). In a similar way, dietary levels of *o,p'*-DDT as high as 40 ppm, giving a dosage level of about 2.1 mg/kg/day in rats, failed to interfere with reproduction and lactation in these animals, although dosage was continued through two pregnancies (Wrenn *et al.*, 1971a).

The report (Heinricks *et al.*, 1971) that *o,p'*-DDT significantly advances puberty, induces persistent vaginal estrus after a period of normal estrous cycles, and causes other reproductive abnormalities in female rats would at first appear inconsistent with the lack of effect of technical DDT or of *o,p'*-DDT on reproduction cited above. The same is true of other effects of *o,p'*-DDT demonstrated by the same investigators (Gellert *et al.*, 1972). The abnormal effects were obtained initially by injecting 1 mg of the *o,p'*-DDT subcutaneously on the second, third, and fourth days of life (counting the day of birth as zero). Because rat pups on the third day weight about 12 gm or less

each, it follows that the subcutaneous dosage was about 83.3 mg/kg/day or more, that is, about 40 times greater than the highest oral dosage of *o,p'*-isomer fed to breeding rats and about 10⁵ times greater than what ordinary people get in their food.

Ottoboni (1969) found that female rats reproduced normally when fed DDT for two generations at dietary levels as high as 200 ppm (about 10 mg/kg/day except during lactation, when intake is increased about threefold). In fact, at a dietary level of 20 ppm, the dams had a significantly longer reproductive life span (14.55 months) than their littermate controls (8.91 months); the number of females becoming pregnant after the age of 17 months and the number of successful pregnancies after that age were significantly different in the two groups (Ottoboni, 1972).

In a study focused mainly on DDT in milk, the full ability of rats to reproduce at a dietary level of 200 ppm was confirmed, and the ability of dams injected intraperitoneally at levels as high as 100 mg/kg/day to rear their young was demonstrated (Hayes, 1976b).

A six-generation test of reproduction in mice showed no effect of DDT at a dietary level of 25 ppm on fertility, gestation, viability, lactation, and survival. A level of 100 ppm produced a slight reduction in lactation and survival in some generations but not all, and the effect was not progressive. A level of 250 ppm was distinctly injurious to reproduction (Kepplinger *et al.*, 1970). The dietary concentrations used determine dosages of 3.33, 13.3, and 33.2 mg/kg/day in nonpregnant, nonlactating, adult, female mice. The intake is much higher in both young and lactating mice. The authors concluded that their study provided no obvious reason for continuing reproduction tests for more than three generations.

Four female dogs of unstated age that previously had received DDT at the rate of 12 mg/kg/day, 5 days/week, for 14 months were bred when they went into heat. The males involved had been fed aldrin (0.15 mg/kg/day) plus DDT (60 mg/kg/day) for 14 months prior to breeding but not during breeding. Two of the females went into heat but failed to become pregnant, and one failed to come into heat during 12 months after feeding stopped. Four of six pups born to the fourth female died within 1 week of birth; the other two were weaned successfully even though only two posterior mammae of the mother were functional (Deichmann *et al.*, 1971b). A three-generation study failed to confirm any of the injuries suggested by the study of four dogs. In the three-generation study, male and female dogs were fed technical DDT from weaning at rates of 0, 1, 5, and 10 mg/kg/day. Observations were made on 135 adult females, 63 adult males, and 650 pups. There were no statistically significant differences among controls and DDT-treated dogs in length of gestation, fertility, success of pregnancy, litter size, or lactation ability of the dams; in viability at birth, survival to weaning, sex distribution, and growth of pups; or in morbidity, mortality, organ/body weight ratios, or gross histological abnormalities in all the animals studied. The only clear difference was that DDT-treated females had their first estrus 2 or 3 months earlier than the control dogs. There was a slight increase in liver/body weight ratio in some DDT-treated animals but the difference was not statistically significant, not

dosage-related, and not associated with any histological change (Ottoboni *et al.*, 1977).

When *p,p'*-DDT was administered to pregnant mice at a rate of 1 mg/kg on days 10, 12, and 17 of gestation, it was not teratogenic but did alter the gonads and decrease the fertility of the young, especially the females (McLachlan and Dixon, 1972). A single dose at the rate of 15 mg/kg or repeated doses of 2.5 mg/kg/day given during pregnancy may be embryotoxic but not teratogenic to mice (Schmidt, 1973). Why one or a few doses during pregnancy may be embryotoxic although the same dosage is harmless when administered during the entire reproductive period is of theoretical but no practical importance.

Teratogenic effects of DDT have not been seen in studies of reproduction, including those for two generations in rats, six generations in mice, and three generations in dogs.

Because of the estrogenic properties of large doses of DDT, the compound was considered as a possible cause of abortion in dairy cattle, but no evidence for a relationship was found (Macklin and Ribelin, 1971). A similar conclusion was reached regarding human abortions (O'Leary *et al.*, 1970).

Behavioral Effects Behavioral changes may be demonstrated in animals receiving DDT daily at rates too low to produce illness. Khairy (1959) was able to detect ataxia in the form of changes in gait in rats that had been fed DDT at dietary levels of 100 ppm or more for 21 days. The results were recorded in terms of the tangent, that is, the ratio of the width and length of step. At a dosage of about 5 mg/kg/day the ratio was less than normal, a change attributed to an exaggeration of the stretch reflex. At dosages of about 10, 20, and 30 mg/kg/day, the ratio was progressively increased above normal as a result of broadening of the gait and shortening of the steps. These same dosage levels did not affect problem-solving behavior or speed of locomotion. The experimental animals were found to be generally less reactive to stress than normal ones. The acoustic startle response of rats is significantly increased after a 12.5 mg/kg dose of *p,p'*-DDT but can be attenuated by phenytoin and an adrenergic receptor antagonist, phenoxybenzamine (Tilson *et al.*, 1985, 1986; Saitoh *et al.*, 1986; Herr *et al.*, 1987), which also decreased DDT-induced myoclonus (Huang and van Voert, 1978). See also Effects on the Nervous System.

Pathology Morphological changes are inadequate to account for death from DDT poisoning. Changes that occur in the liver are discussed in Section 15.2.3.2. Mild to moderate morphological changes have been reported in the kidneys of animals that had received massive single doses or repeated doses; examples are fatty degeneration, necrosis, and calcification (Lillie *et al.*, 1947; Stohlman and Lillie, 1948) or slight brown pigmentation of the convoluted tubular epithelium (Fitzhugh and Nelson, 1947). However, it sometimes has happened that a complete absence of change in the kidney has been reported in connection with other studies carried out in the same laboratories (Lillie and Smith, 1944; Nelson *et al.*, 1944).

Treatment of Poisoning in Animals The more successful studies of treatment of animals poisoned by DDT involve the nervous system. Smith and Stohlman (1944) noted the possibility that narcotics in general may exhibit an antagonism to DDT. Rats survived on a diet containing 1000 ppm DDT for 90 days when they received cyclohexanone in the same diet at the rate of 2000 ppm but were uniformly killed in a shorter period when they received DDT at the same rate but without cyclohexanone. Later, it was shown that cyclohexanone offers no protection when used as a solvent for single massive doses of DDT (Deichmann *et al.*, 1950).

Smith and Stohlman (1945) later showed that, when rats were given urethane and, to a lesser extent, sodium dilantin as required after the onset of illness, the animals were protected from poisoning. Sodium amobarbital gave slight benefit, sodium phenobarbital a doubtful benefit, and paraldehyde no protection at all. All drugs were given intraperitoneally except paraldehyde, which was given by stomach tube. The mortality of rats treated with urethane was 12.5% and that of their controls was 80%. A total dosage of 1.2–2.5 gm/kg spread over a period of 1–3 days was found most satisfactory. Sodium dilantin reduced mortality to 46.7%, compared to 96.7% for the controls. The smallest effective dosage was 200–250 mg/kg, a value very close to the LD 50, which, under the conditions of the test, was 300 mg/kg.

Läuger *et al.* (1945a,b) also found that sodium phenobarbital was of questionable value in treating rats poisoned by DDT. However, completely different results were seen in larger animals. Philips and Gilman (1946) found phenobarbital by far the most outstanding remedy they tested. In a dosage well below the anesthetic level, it not only prevented death in many instances but also controlled tremor and convulsions. Signs of illness were more readily controlled in dogs and cats than in monkeys, which required nearly a full anesthetic dosage before tremors completely disappeared.

Magnesium sulfate did not reduce mortality in poisoned dogs and cats, although it did control tremors and convulsions briefly. Sodium bromide was entirely ineffective. Mortality was reduced with urethane, but a full anesthetic dosage was required to control tremor and convulsion. Similarly, sodium barbital and sodium pentobarbital controlled symptoms only when given in full anesthetic doses and even then did not greatly reduce mortality. 5,5-Diphenylhydantoin (phenytoin), when given to rats before they received DDT, reduced the lethal action without showing a notable effect on the signs of poisoning; it was not effective in cats. More recently, Tilson *et al.* (1985, 1986) have reported that phenytoin attenuates the tremor produced in rats by DDT and permethrin but not by lindane and chlordecone.

Vaz and his colleagues (1945) were apparently the first to note the antidotal effect of calcium in DDT poisoning. Dogs were given DDT orally as a 10% oily solution at a daily dosage of 100 mg/kg until signs of intoxication appeared. The same dosage could then be repeated to produce intense symptomatology from which the animals would recover spontaneously in 12–24 hr. For the actual tests, a larger challenge

dosage of DDT (150–200 mg/kg) was used. Each dose of calcium gluconate (30 ml of a 10% solution) was injected intravenously into dogs weighing 8–18 kg. Dogs that were injected with calcium gluconate daily for 4 days and challenged with a large dose of DDT on the fourth day developed no symptoms or only slight ones. Dogs receiving a single dose of calcium gluconate showed symptoms of short duration and survived following a dosage of DDT large enough to kill two controls.

Koster (1947) studied cats poisoned by the intravenous injection of a soya lecithin–corn oil emulsion of DDT. A comparison was made of several aspects of intoxication, including number of convulsions, general severity (tremors, prostration, dyspnea), duration, and mortality. Both calcium gluconate and sodium gluconate reduced mortality but not severity. Gluconic acid increased the survival time, reduced mortality, but did not reduce convulsions or severity. Calcium chloride reduced convulsions but not mortality or tremors. Molecular equivalent doses of the candidate antidotes were used. Gluconic acid and its two salts were effective against an LD 95 dosage of DDT. The lifesaving capacity of calcium gluconate at a rate of 40 mg/kg was confirmed by Judah (1949), even though he found normal blood calcium values in most poisoned but unmedicated animals. One animal showed a high calcium value, and Cameron and Burgess (1945) reported a similar result. It has been suggested that increased blood calcium may be associated with acidosis caused by the accumulation of lactate.

Calcium has, then, an antidotal action against DDT in intact animals of several species. The suppression by calcium of the effect of DDT on the isolated nerve and muscle of the rat has been demonstrated (Eyzaguirre and Lilienthal, 1949). The hypothesis has been advanced (Welsh and Gordon, 1946; Gordon and Welsh, 1948) that certain neurotoxins, including DDT, act by delaying the restoration of calcium ions to a surface complex following breaking of the chelate linkage of calcium ions to surface polar groups by an initial exciting impulse. This action of the neurotoxin is conceived as depending largely on its physical rather than on its chemical properties. The hypothesis is helpful in explaining the fact that a wide variety of chemically unrelated compounds produce repetitive responses in excitable tissue and also the fact that many compounds that show a high toxicity for arthropods and mammals are fat-soluble and chemically relatively inert. It has been pointed out that this hypothesis postulates a very localized action of calcium at the nerve cell membrane; the hypothesis is not inconsistent with the finding that the blood calcium of poisoned animals may be unchanged or even increased. On the other hand, calcium may help to offset the effects of DDT on calcium-dependent ATPases, especially in the neuronal axons (see Biochemical Effects, p. 755).

Having observed the effect of DDT on the metabolism of glucose and glycogen, Läuger and his colleagues (1945a,b) investigated the use of glucose as an antidote. All of the 10 dogs given 2000 mg of DDT per kilogram of body weight orally in the form of an oil solution died within 8–24 hr. Five of the 10 dogs treated with one or more 20-ml doses of 20%

glucose survived the same dosage of DDT. The glucose was given intravenously in most instances.

Koster (1947) found that glucose given before or after an LD 33 dosage reduced convulsions and mortality and, when given before the poison, reduced tremors, prostration, and dyspnea in cats. Glucose, unlike gluconic acid and its sodium and calcium salts, was ineffective against an LD 95 dosage except to increase the time of survival. Insulin given intramuscularly 16–25 min before DDT increased the survival time and the severity of poisoning but did not affect mortality or convulsions. When given 53–130 min before DDT, insulin reduced convulsions in animals that died but increased convulsions, tremors, and other disorders in the survivors.

15.3.1.3 Toxicity to Humans

Experimental Oral Exposure Table 15.8 summarizes the effects of one or a few carefully measured oral doses of DDT. The results are consistent with those in accidents reported by Garrett (1947) and Hsieh (1954) in which it was possible to

Table 15.8
Summary of the Effects of One or a Few Oral Doses of DDT on Volunteers

Dose (mg) and formulation	Result	Reference
250 × 9, suspension	no effect	Domenjoz (1944)
1500, butter solution	no effect, but mice killed when fed 6 and 12 hr after dose	MacCormack (1945)
500, oil solution	no clinical effect	Neal <i>et al.</i> (1946)
770, oil solution	no clinical effect; DDA measured in urine	Neal <i>et al.</i> (1946)
250, suspension	none except slight disturbance of sensitivity of mouth	Velbinger (1947a,b)
250, oil solution	variable hyperesthesia of mouth	Velbinger (1947a,b)
500, oil solution	variable hyperesthesia of mouth	Velbinger (1947a,b)
750, oil solution	disturbance of sensitivity of lower part of face; uncertain gait; peak reaction (6 hr after ingestion) characterized by malaise, cold moist skin, and hypersensitivity to contact; reflexes normal	Velbinger (1947a,b)
1000, oil solution	same as above; no joint pains, fatigue, fear or difficulty in seeing or hearing	Velbinger (1947a,b)
1500, oil solution	prickling of tongue and around mouth and nose beginning 2.5 hr after dose; disturbance of equilibrium; dizziness; confusion; tremor of extremities; peak reaction (10 hr after ingestion) characterized by great malaise, headache, and fatigue; delayed vomiting; almost complete recovery in 24 hr	Velbinger (1947a,b)

estimate accurately the amount ingested. It may be concluded that a single dose at the rate of 10 mg/kg produces illness in some but not all subjects even though no vomiting occurs. Smaller doses generally produce no illness, although a dosage of 6 mg/kg produced perspiration, headache, and nausea in a man who was sickly and who was hungry at the time of eating. Persons who were made sick by 10 mg/kg have not shown convulsions, but convulsions have occurred in accidents when the dosage level was 16 mg/kg or greater (Hsieh, 1954). Rarely, a dosage as high as 20 mg/kg may be taken without apparent effect (MacCormack, 1945). Dosages at least as high as 285 mg/kg have been taken accidentally without fatal result (Garrett, 1947). However, large doses lead to prompt vomiting, so the amount actually retained cannot be determined accurately.

In acute poisoning a slight decrease in hemoglobin and a moderate leukocytosis without any constant deviation in the differential white count have been observed in volunteers (Velbinger, 1947a,b). These findings are considered secondary to the neurological effects.

It has been noted in the course of tests with volunteers that dilute colloidal aqueous suspensions of DDT are odorless and tasteless (Domenjoz, 1944; Hoffman and Lendle, 1948). Saturated alcoholic solutions of DDT have a weak aromatic taste, or rather odor. Some people find these solutions slightly anesthetic to the tongue (Hoffman and Lendle, 1948). The taste of DDT in vegetable oil is so slight that many persons cannot identify capsules containing 0, 3.5, and 35 mg of DDT when they are presented separately but can arrange them in proper order when one of each is available for comparison.

The possible clinical effects of many repeated doses of DDT were first explored by Fennah (1945). Because of his interest in predicting the results of indiscriminate use, he expressed the exposures in terms of environmental levels rather than in dosage units. The exposures were clearly higher than those ordinarily encountered. In one test, lasting a total of 11.5 months, Fennah daily inhaled 100 mg of pure DDT and drank water dusted at the rate of 3240 mg/m². Much of the inhaled dust must have been deposited in the upper respiratory tract and swallowed. Later, for 1 month Fennah ate food all of which had been sprayed at the rate of 2160 mg/m² after it had been served. No ill effect of any kind was observed.

Some later studies of DDT in volunteers have been designed to explore the details of storage and excretion of the compounds in humans and to search for possible effects of doses considered to be safe. In the first of these studies, men were given 0, 3.5, and 35 mg/person/day. These administered dosages plus DDT measured in the men's food resulted in dosage levels of 0.0021–0.0034, 0.038–0.063, and 0.36–0.61 mg/kg/day, respectively, the exact value depending on the weight of each individual. Six volunteers received the highest dosage of technical DDT for 12 months, and three received it for 18 months. A smaller number of men ingested the lower dosage of technical DDT or one of the dosages of *p,p'*-DDT for 12–18 months. No volunteer complained of any symptom or showed by the tests any signs of illness that did not have an easily

recognizable cause clearly unrelated to the exposure of DDT. At intervals, the men were given a systems review, physical examination, and a variety of laboratory tests. Particular attention was given to the neurological examination and liver function tests, because the major effects of DDT in animals involve the nervous system and the liver (Hayes *et al.*, 1956).

The same result was obtained in a second study in which the same dosages were given for 21 months and the volunteers were observed for a minimum of 27 additional months (Hayes *et al.*, 1971).

In the first study, the storage of DDT was proportional to dosage, but there was a then unexplained difference in the storage of the *p,p'*-isomer and of technical DDT. Following dosing for 12 months, the pure material was stored in fat at an average concentration of 340 ppm, but the technical material was stored at an average of only 234 ppm. The difference was statistically significant for the 3.5 mg/person/day dosages given for 3–6 and for 7–18 months. The difference was significant for the 35 mg/person/day doses after 7–18 months of dosing but not after only 3–6 months.

Men who ate *p,p'*-DDT showed a definite increase in the absolute amount of DDE stored. After 6 months at a dosage of 35 mg/person/day, eight men showed an average DDE fat storage of 32.6 ± 7.0 ppm as compared to 12.3 ± 1.5 ppm for the same individuals upon entering the investigation. There was a further increase of DDE storage as exposure progressed. However, DDT was stored in so much greater concentration that the relative storage of DDE decreased sharply. Thus, after 6 months at a dosage of 35 mg/person/day, eight men stored only 14% of their total DDT-derived material in the form of DDE as compared to 65% for the same persons at the beginning of the investigation.

The storage of DDE by men who ate technical DDT presented a different picture. Until 18 months after exposure, there was no clear evidence that these men stored any more DDE after exposure than they did before. However, at 18 months the only three samples available showed DDE concentrations ranging from 28 to 85 ppm, all substantially above general population levels. Thus, both the total amount stored and the rate at which DDT converted to DDE served to distinguish the metabolism of *p,p'*-DDT and technical DDT in humans (Hayes *et al.*, 1956). This was true even though later study showed that the concentration of DDE in serum increased immediately in persons ingesting technical DDT at rates of 10 and 20 mg/person/day. Of course, daily values were subject to considerable variation, but the upward slopes of the graphs recording the results were apparent in 60 days or less and apparently the graphs were straight throughout the 5-month feeding period. Under the same conditions, the level of DDT in serum increased within 1 day and continued to increase in a curvilinear fashion for 5 months (Apple *et al.*, 1970). A similar rapid increase reaching its maximum in 30 hr after a single exposure has been observed in workers (Edmundson *et al.*, 1969a). The more rapid excretion of *o,p'*-DDT was demonstrated by Morgan and Roan (1972).

In a second study in which the volunteers received 0, 3.5, and 35 mg/person/day, the storage of DDT was again propor-

Table 15.9
Storage of DDT in Volunteers

Type of DDT	Added dosage (mg/person/day)	Concentration of DDT ^a				Significance of difference (<i>p</i>)
		First study ^b 11 months or more (ppm)		Second study ^c 21.5 months (ppm)		
Technical	0	8–17	(12.5 ± 4.5)	16–30	(22.0 ± 2.9)	>0.1
	3.5	26–33	(23.8 ± 1.4)	59–76	(50.2 ± 5.6)	<0.025
	35	101–367	(234 ± 21.4)	105–619	(281 ± 79.5)	>0.4
Recrystallized	35	216–466	(340 ± 36.4)	129–659	(325 ± 62.2)	>0.2

^a Range, mean ± SEM.

^b Hayes *et al.* (1956).

^c Hayes *et al.* (1971).

tional to dosage. Although, in this instance also, the storage of technical DDT was less than that of *p,p'*-DDT, the difference was not statistically significant. The real but very gradual accumulation of DDE was confirmed. A steady state of storage was approached later in the second study (18.8–21.5 months) than in the earlier one (about 12 months). The second study was superior in that more men were observed for a longer period but inferior in that dosing was less regular. Because of the latter difficulty, it seems impossible to decide whether 12 months or 21.5 months is a more valid estimate of the time necessary for people to approach a steady state of storage when intake is uninterrupted and unvarying in amount. It is interesting that the storage levels eventually reached at the same dosage in the two studies were statistically indistinguishable in most instances (see Table 15.9). In the one instance in which a statistical difference existed, the greater storage by men in the second study may have been explained by the fact that some of them inadvertently received higher doses than intended.

DDT was lost slowly from storage in fat after dosing was stopped. The concentration remaining following 25.5 months of recovery was from 32 to 35% of the maximum stored for those who had received 35 mg/person/day but was 66% for those who had received only 3.5 mg/person/day, indicating slower loss at lower storage levels (Hayes *et al.*, 1971).

Morgan and Roan (1971) fed volunteers not only technical DDT but also *p,p'*-DDE and *p,p'*-DDD. They found that DDE is stored more tenaciously than the other compounds in humans, the order being *p,p'*-DDE > *p,p'*-DDT > *o,p'*-DDT ≥ *p,p'*-DDD. The slow metabolism of DDT to DDE was confirmed. It was noted that *p,p'*-DDT is lost from storage in adipose tissue much more slowly in humans than in the monkey, dog, or rat.

Less than 18% *p,p'*-DDT and *p,p'*-DDE is carried in human erythrocytes. In plasma of ordinary fat content, less than 1% of all DDT-related compounds is carried by the chylomicrons. Instead, these compounds are carried by proteins and are undetectable in plasma from which protein has been precipitated. Following ultracentrifugation, *p,p'*-DDT and *p,p'*-DDE are found mainly in the triglyceride-rich, low-density and very low-density lipoproteins. Following continuous electrophore-

sis, these compounds are found mainly in association with plasma albumin and α -globulins (Morgan *et al.*, 1972).

DDA is the main urinary metabolite of DDT. In humans, it was found first in a volunteer by Neal *et al.* (1946), who reported that, following ingestion of 770 mg of *p,p'*-DDT, excretion rose sharply to 4.0 mg/day during the second 24-hr period, decreased rapidly on the third and fourth days, decreased gradually thereafter, but was still above baseline on day 14. Judging from a graph, the highest concentration was about 2.6 ppm.

Much later studies in volunteers who received smaller but repeated doses confirmed the very rapid rise in excretion of DDA (Roan *et al.*, 1971; Hayes *et al.*, 1971) and showed that a steady state of excretion was reached after about 6–8 months. During a 56-week period of continued dosing after equilibrium was fully established, the concentration of DDA associated with technical DDT at the rate of 35 mg/person/day varied from 0.18 to 9.21 ppm and averaged 2.98 ppm; corresponding values for *p,p'*-DDT were 0.40–6.27 ppm with a mean of 1.88 ppm. Thus technical DDT, as compared to *p,p'*-DDT, was excreted more effectively and stored less.

During the latter half of the dosing period, it was possible in the two groups receiving recrystallized and technical DDT at the rate of 35 mg/person/day to account for an average of 13 and 16%, respectively, of the daily dose in terms of urinary DDA. The excretion of DDA was relatively constant in each individual, but marked differences were observed between men receiving the same dose. For example, over the period of 56 weeks the highest rate measured for one man was 0.16 mg/hr while the lowest rate for another in the same group was 0.15 mg/hr. Their mean rates during this period were 0.089 and 0.269 mg/hr, respectively. The difference was highly significant (*P* < 0.001) (Hayes *et al.*, 1971).

Experimental Dermal Exposure Depending on dosage, oral administration of DDT to volunteers has produced either no illness or brief poisoning entirely similar to that seen in experimental animals. The oral dosage necessary to produce any clinical effect was almost always 10 mg/kg or more. It is a strange coincidence that, in two studies involving only three

subjects in all, experimental dermal exposure to DDT was followed by fatigue, aching of the limbs, anxiety or irritability, and other subjective complaints. Recovery was delayed a month or more (Wigglesworth, 1945; Case, 1945). In neither study was there an independent control. Although the dosage was unmeasured, the amounts of DDT absorbed must have been much smaller than those involved in the oral tests. One of the studies involved self-experimentation by one man. A similar but somewhat more severe test on six volunteers produced no toxic or irritant effect at all (Dangerfield, 1946). In view of all other experiments and extensive practical experience, it must be concluded that the illnesses reported by Wigglesworth and Case were unrelated to DDT.

With the exceptions just mentioned, dermal exposure to DDT has been associated with no illness and usually no irritation (Domenjoz, 1944; Cameron and Burgess, 1945; Dangerfield, 1946; Chin and T'Ant, 1946; Wasicky and Unti, 1944; Draize *et al.*, 1944; Haag *et al.*, 1948; Fennah, 1945). In fact, Hoffman and Lendle (1948) reported that even subcutaneous injection of colloidal suspensions of DDT in saline in concentrations up to 30 ppm caused no irritation. Zein-el-Dine (1946) reported that DDT-impregnated clothing caused a slight, transient dermatitis, but the method of impregnation was not stated and the absence of solvent was not guaranteed. Other more thorough studies of DDT-impregnated clothing have found it nonirritating (Domenjoz, 1944; Cameron and Burgess, 1945).

Chin and T'Ant (1946) applied small pads impregnated with different formulations of DDT to the inner surface of the forearm of 32 volunteers whose cutaneous sensation had previously been measured for a period of 5 weeks. Pads impregnated with all the elements of the formulation except DDT were applied to the corresponding position on the other arm as a control. Powdered DDT and 5% solutions of DDT showed little effect. Ten percent and 20% solutions in olive oil and petroleum showed no remarkable effect on sensation of pain, cold, or heat but reduced tactile sensation in most cases so that the minimal pressure that could arouse this sensation was 1–2.5 gm/cm² higher than in the control.

Experimental Respiratory Exposure Neal *et al.* (1944) reported almost continuous daily exposure to aerosols sufficient to leave a white deposit of DDT on the nasal vibrissae of the volunteers. This exposure produced moderate irritation of the nose, throat, and eyes. Except for this irritation during exposure, there were no symptoms, and laboratory tests and physical examination, including neurological evaluation, failed to reveal any significant changes. The studies by Fennah (1945) that involved both respiratory and oral exposure produced no detectable ill effect, as discussed above. Stammers and Whitfield (1947) reported tests in which volunteers were exposed to DDT dispersed into the air either by volatilizing units or by continuously or intermittently operated aerosol dispensers. In some instances, a slight odor and some dryness of the throat were noticed, but otherwise the results were negative.

Therapeutic Use The use of DDT for treating human body lice, head lice, and scabies has been reviewed by Simmons (1959). Obviously, these uses offered a possibility of dermal absorption, but such absorption of dry DDT is very limited. Persons who had DDT blown into their clothing as they wore it must have inhaled some of the compound, and this was especially true of persons who used hand or power equipment to apply the dust to hundreds of people per day in mass delousing stations set up to control typhus. However, the dosages absorbed cannot have been so large as in some instances in which DDT has been administered by mouth. Even smaller absorbed dosages for the general population were involved in the use of DDT for the control of other vector-borne diseases, especially malaria. These facts must not lead us to forget the tremendous contribution that DDT has made to human health through control of the vectors of typhus, malaria, plague, and several lesser diseases (Spindler, 1983; Coulston, 1985).

DDT has been used on an experimental basis at oral dosage rates varying from 0.3 to 3 mg/kg/day for periods up to 7 months in an attempt to decrease serum bilirubin levels in selected patients with jaundice. No side effects were observed. No improvement was noted in patients with jaundice based on cirrhosis who had no demonstrated liver enzyme deficiency. However, in a patient with familial, nonhemolytic, unconjugated jaundice based on a deficiency of glucuronyltransferase, treatment with DDT rapidly reduced the plasma bilirubin level to the normal range and relieved the patient of nausea and malaise from which he had suffered intermittently. The liver function tests as well as other laboratory findings remained normal. The improvement was maintained during the 6 months when DDT was administered and had persisted for 7 additional months at the time the report was written. In this case, a dosage of 1.5 mg/kg/day produced a steady rise in plasma levels of *p,p'*-DDT from an initial level of 0.005 ppm to a maximum of 1.33 ppm at the end of treatment. At this time, the concentration in body fat was 203 ppm. Plasma levels fell slowly after dosing was stopped (Thompson *et al.*, 1969). The highest daily intake in this series was six times greater than the highest level administered in earlier studies of volunteers and about 7500 times greater than the DDT intake of the general population. The highest value for *p,p'*-DDT in serum observed in the entire series was 1.330 ppm, compared to 0.996 ppm, the highest value reported by Laws *et al.* (1967) for formulation-plant workers. A lesser induction of the microsomal enzymes has been observed in workers also (Kolmodin *et al.*, 1969; Poland *et al.*, 1970).

Rappolt (1970) used a single dose of 5000 mg of DDT to promote the metabolism of phenobarbital, of which his three patients had taken an overdose. The treatment appeared useful. Neither Rappolt nor Thompson encountered any side effects of DDT. However, in addition to whatever action it may have had in promoting the metabolism of phenobarbital, the DDT administered by Rappolt must have acted largely as a pharmaceutical antidote for the barbiturate. The largest dose previously administered intentionally was 1500 mg, which caused

moderate poisoning in a volunteer, who, of course, had received no barbiturate (see Table 15.8).

Accidental and Intentional Poisoning The earliest symptom of poisoning by DDT is hyperesthesia of the mouth and lower part of the face. This is followed by paresthesia of the same area and of the tongue and then by dizziness, an objective disturbance of equilibrium, paresthesia and tremor of the extremities, confusion, malaise, headache, fatigue, and delayed vomiting. The vomiting is probably of central origin and not due to local irritation. Convulsions occur only in severe poisoning.

Onset may be as soon as 30 min after ingestion of a large dose or as late as 6 hr after smaller but still toxic doses. Recovery from mild poisoning usually is essentially complete in 24 hr, but recovery from severe poisoning requires several days. In two instances, there was some residual weakness and ataxia of the hands 5 weeks after ingestion.

Involvement of the liver has been mentioned in only a small proportion of cases of accidental poisoning by DDT. In three men who ate pancakes made with DDT and who ingested 5000–6000 mg each, slight jaundice appeared after 4–5 days and lasted 3–4 days (Naevested, 1947). Hepatic involvement and convulsions were reported in an unsuccessful attempt at suicide by ingesting DDT and lindane (Eskenasy, 1972).

Cases of individual and suicidal poisoning in which effects were clearly caused by DDT are summarized in Table 15.10. All of these cases involved ingestion. The signs and symptoms of poisoning were entirely consistent with those observed in volunteers, except that the spectrum of effects was broader because some of the accidental and suicidal doses were very high. A few persons apparently have been killed by uncomplicated DDT poisoning, but none of these cases was reported in detail. Death has been caused much more frequently by the ingestion of solutions of DDT, but in most of these instances the signs and symptoms were predominantly or exclusively those of poisoning by the solvent (Hayes, 1959a). This does not mean that the toxicity of the solvent always predominates. For example, the recurrent convulsions in a case reported by Cunningham and Hill (1952), though more characteristic of poisoning by one of the cyclodienes, was certainly not typical of solvent poisoning. A 2-year-old child drank an unknown quantity of fly spray of which 5% was DDT, but the nature of the other active ingredients or the solvent was unknown. About 1 hr after taking the material, the child became unconscious and had a generalized, sustained convulsion. Convulsions were present when the child was hospitalized 2 hr after taking the poison, but the fits were controlled by barbiturates and other sedatives. Convulsions reoccurred on day 4 and again on day 21 but were stopped each time following renewal of treatment. On day 12, it was noted that the patient was deaf. Hearing began to improve about day 24 and was normal, as were other neurological and psychic findings, when the patient was seen about 2.5 months after the accident.

Clinical effects of one toxicant may be modified by

Table 15.10
Summary of the Effects of the Accidental or Suicidal Ingestion of DDT

Individual dose (mg), formulation, and number of persons	Results and reference
300–4500, in food, 1 man	onset in 1 hr; vomiting; restlessness; headache; heart weak and slow; recovery next day (Muhlens, 1946)
Unknown dose, in tarts, 25 men	onset in 2–2.5 hr; all weak and giddy; 4 vomited; 2 hospitalized; 1 confused, incoordinated, weak; one with palpitations and numbness of hands; recovery in 24–48 hr (Mackeras and West, 1946)
5000–6000, in pancakes, 3 men	onset 2–3 hr; throbbing headache; dizziness; incoordination; paresthesias of extremities; urge to defecate; wide, nonreacting pupils; reduced vision; dysarthria; facial weakness; tremor; ataxic gait; reduced sensitivity to touch; reduced reflexes; positive Romberg; slightly low blood pressure and persistent irregular heart action; partial recovery in 2–3 days, but slight jaundice appeared 4–5 days after ingestion and lasted 3–4 days; all normal 19 days after poisoning except irregular heart action in one (Naevested, 1947)
2000, in pancakes, 2 men	no illness (Naevested, 1947)
Up to 20,000, in bread, 28 men	onset in 30–60 min in those most severely affected; men first seen 2–3 hr after ingestion; in spite of severe early vomiting that reduced the effective dose, severity of illness and especially intensity of numbness and paralysis of extremities proportional to amount of DDT ingested; all but 8 men recovered in 48 hr; 5 others fully recovered in 2 weeks, but 3 men still had some weakness and ataxia of their hands 5 weeks after ingestion (Garrett, 1947, 1950)
Unknown dose, in flour, about 100 women	onset about 3.5 hr after ingestion; total of about 85 cases of which 37 were hospitalized; symptoms mild and similar to those in earlier outbreaks except gastrointestinal disturbance in most severe cases included abdominal pain and diarrhea as well as nausea; most fully recovered in 24 hr (Jude and Girard, 1949)
Unknown dose, 14 cases	symptoms in established cases similar to those reported earlier (Francone <i>et al.</i> , 1952)
286–1716, in meatballs, 8 cases, 11 exposed	with the exception of one man who was already sick when he received a dosage of 6 mg/kg, poisoning did not occur at dosages of 5.1–10.3 mg/kg. Ingestion of 16.3–120.5 mg/kg produced excessive perspiration, nausea, vomiting, convulsions, headache, increased salivation, tremors, tachycardia, and cyanosis of the lips. Onset varied from 2 to 6 hr, depending on dosage. Recovery required as much as 2 days (Hsieh, 1954).
Unknown dose, 1 case	death 13 hr after suicidal ingestion (Committee on Pesticides, 1951)
Unknown dose, 22 unrelated cases	22 separate cases, including 15 attempted suicides; some complicated by solvents; 3 deaths (Committee on Pesticides, 1951)

combining it with another. For example, one would not expect prolonged illness from DDT at a rate of 27 mg/kg. However, when DDT and lindane were ingested in a suicidal attempt at dosages thought to be 27 and 18 mg/kg respectively, clinical remission of convulsions and of liver involvement was delayed until day 20, and the EEG did not return to normal until day 39 (Eskenasy, 1972).

What little is known about the effect of DDT on the human heart fails to show whether cardiac arrhythmia might be a possible cause of death in acute poisoning, as is true in some species of laboratory animals. Palpitations, tachycardia, and "irregular heart action" have been noted in some but not all cases of acute poisoning (Mackerras and West, 1946; Naevested, 1947; Hsieh, 1954).

There have been no accidents or suicides involving respiratory or dermal exposure leading to recognized signs and symptoms of DDT poisoning. This is true even though sufficient respiratory exposure to aerosols or sufficient dermal exposure to solutions can cause poisoning in animals, and the difference is certainly one of dosage.

Use Experience The safety record of DDT is phenomenally good [Coulston, 1985; Food and Agriculture Organization/World Health Organization (FAO/WHO), 1985]. It has been used for mass delousing in such a way that the bodies and inner clothing of thousands of people of all ages and states of health were liberally dusted with the compound. By necessity, the applicators worked in a cloud of the material. Other applicators have sprayed the interior of hundreds of millions of homes in tropical and subtropical countries under conditions that Wolfe *et al.* (1959) showed involved extensive dermal and respiratory exposure. A smaller number of people have made or formulated DDT for many years. Extensive experience and numerous medical studies of groups of workers have been reviewed (Hayes, 1959a). Dermatitis was commonly observed among workers who used DDT solutions. The rashes were clearly due to the solvent, especially kerosene. As often happens with rashes caused by petroleum distillates, they were most severe in people when they first started work and cleared in a few days unless contamination was exceptionally severe. A smaller number of workers experienced mild narcotic effects (vertigo and nausea) from solvents when working in confined spaces. Gil and Miron (1949) reported that some persons suffered temporary irritability, fatigue, and other ill-defined symptoms after exposure in the dusty atmosphere of a delousing station, but the relation of these atypical findings to DDT was not clear. With these exceptions due largely to solvents, no illnesses clearly attributable to the formulations, much less to DDT, were revealed by the early studies.

Mild moderate poisoning by DDT itself may have occurred among a group of factory workers exposed to air concentrations of 500–4200 mg/m³, but no measurements were made of DDT in blood, fat, or urine. The workers complained of paresthesia of the extremities, headache, dizziness, and some other difficulties less clearly linked to DDT (Aleksieva *et al.*, 1959). Even higher concentrations in air have been associated with

tremor of the tongue and hands as well as with numerous subjective findings (Burkatzkaya *et al.*, 1961).

Ortelee (1958) carried out clinical and laboratory examinations of 40 workers, all of whom were exposed to a number of other pesticides. They had been employed at this work with heavy exposure for 0.4–6.5 years with slightly less exposure for as much as 8 years. Exposure was so intense that during working hours many of the men were coated with a heavy layer of concentrated DDT dust. By comparing their excretion of DDA with that of volunteers given known doses of DDT, it was possible to estimate that the average absorbed dosages of three groups of the workers with different degrees of occupational exposure were 14, 30, and 42 mg/person/day. With the exception of the excretion of DDA and the occurrence of a few cases of minor irritation of the skin and eyes, no correlation was found between any abnormality and exposure to the insecticide. Since very large doses of DDT injure the nervous system and liver of experimental animals, special attention was given to a complete neurological examination and to laboratory tests for liver function. Although a few abnormalities were revealed, none related to DDT was detected.

Laws *et al.* (1967) studied 35 men employed from 11 to 19 years in a plant that had produced DDT continuously and exclusively since 1947 and, at the time of the study, produced 2722 metric tons per month. Findings from medical history, physical examinations, routine clinical laboratory tests, and chest x-ray films did not reveal any ill effects attributable to exposure to DDT. No case of cancer or blood dyscrasia was found among the 35 heavily exposed workers in a DDT factory, nor did the medical records of 63 men who had worked there for more than 5 years reveal these diseases. Two men were employed who had a history of successfully treated cancer before they came to work, but no employee had contracted cancer during the 19 years the plant had operated; during this period, the work force varied from 110 to 135. A study of liver function of the heavily exposed men is discussed near the end of this section.

Measurement of storage offered direct evidence of the men's heavy exposure. The overall range of storage of the sum of isomers and metabolites of DDT in the men's fat was 38–647 ppm, compared to an average of 8 ppm for the general population. Based on their storage of DDT in fat and excretion of DDA in urine, it was estimated that the average daily intake of DDT by the 20 men with high occupational exposure was 17.5–18 mg/person/day, compared to an average of 0.028 mg/person/day then found for the general population. There was significant correlation ($r = +0.64$) between the concentrations of total DDT-related material in the fat and serum of the workers. The concentration in fat averaged 338 times greater than that in serum—a factor about three times greater than that for people without occupational exposure. Compared to people in the general population, workers were found to store a smaller proportion of DDT-related material in the form of DDE; the difference was shown to be related chiefly to intensity rather than duration of exposure. DDE is relatively much less important and DDA much more important as excretory products in

Table 15.11
Average Concentration of DDT and DDE in Fat and Serum and of DDA in the Urine of Workers Engaged in the Manufacture, Formulation, or Use of DDT

Tissue	Number of workers	DDT (ppm)	DDE (ppm)	DDA (ppm)	Total as DDT (ppm)	Estimated exposure (mg/person/day)	Reference
Fat	1	648	437		1,131		Hayes <i>et al.</i> (1956)
Urine	10			0.57		14	Ortelee (1958)
Urine	16			1.7		30	Ortelee (1958)
Urine	13			2.9		42	Ortelee (1958)
Fat	3	51	44		98	3.6	Laws <i>et al.</i> (1967)
Fat	12	74	50		130	6.2	Laws <i>et al.</i> (1967)
Fat	20	161	91		263	18	Laws <i>et al.</i> (1967)
Serum	3	0.2113	0.1968		0.5412	6.3	Laws <i>et al.</i> (1967)
Serum	12	0.1420	0.1454		0.3548	8.4	Laws <i>et al.</i> (1967)
Serum	20	0.3020	0.2719		0.7371	17.5	Laws <i>et al.</i> (1967)
Urine	3			0.41			Laws <i>et al.</i> (1967)
Urine	12			0.6			Laws <i>et al.</i> (1967)
Urine	20			1.27			Laws <i>et al.</i> (1967)
Serum	18	0.573	0.506				Poland <i>et al.</i> (1970)
Serum	56	0.004 ^{a,b}	0.052 ^{a,b}				Morgan and Roan (1974)
Serum	32	0.002 ^b	0.026 ^b				Morgan and Roan (1974)
Serum	32	0.004 ^b	0.047 ^b				Morgan and Roan (1974)
Serum	32	0.009 ^b	0.075 ^b				Morgan and Roan (1974)
Serum	31	0.052 ^b	0.222 ^b				Morgan and Roan (1974)
Serum	5	0.004 ^a	0.021 ^a				Clifford and Weil (1972)
Serum	10	0.022	0.055				Clifford and Weil (1972)
Serum	4	0.087	0.072				Edmundson <i>et al.</i> (1970)
Blood	154	0.128	0.250				Edmundson <i>et al.</i> (1969a,b)
Urine				0.080			Edmundson <i>et al.</i> (1975)
Plasma	23				0.0389		Gracheva (1969)
Fat	18				5.2–45.2		
Serum	21	0.021	0.013				Keil <i>et al.</i> (1972a)
Blood	44				0.761		WHO (1973)
Blood	100				1.273		WHO (1973)
Blood	64	0.024	0.016				Violante <i>et al.</i> (1986)

^a Control group.

^b Approximately equal groups arranged by degree of storage.

occupationally exposed men than in men of the general population.

After Laws *et al.* (1967) had completed their study, it was found that the 36 most heavily exposed workers involved had fathered 58 children before they began working at the DDT factory and 93 children afterward (Wilcox, 1967).

By far the largest number of heavily exposed workers whose health has been investigated are those associated with malaria control in Brazil and India (WHO, 1973). In Brazil, periodic clinical examinations were made of 202 sprayers exposed to DDT for 6 or more years, 77 sprayers exposed for 13 years ending in 1959, and 406 controls. In the first examination carried out in 1971, minor differences between exposed and nonexposed groups were observed in some neurological tests, but this result was not confirmed by the second examination in the same year or by subsequent examinations. During a 3-year period, a survey of illnesses requiring medical care during the 6 months preceding each periodic medical examination failed to demonstrate any difference between exposed and control groups. A relatively small number of analyses indicated that the concentration of DDT in the blood of sprayers was about three times higher than that of controls.

In India, the blood levels of 144 sprayers were 7.5–15 times greater than those in controls and were at least as high as those reported for workers who make and formulate DDT elsewhere (see Table 15.11). When the sprayers were examined, no differences from controls were found except that knee reflexes were brisker, slight tremor was more often present, and a timed Romberg test was more poorly performed by the sprayers. The positive results led to the selection of 20 men for reexamination by a neurologist, who concluded that the differences found initially were not real or that the tests had returned to normal within the few months between the two examinations. In any event, the signs were not dosage related, since they showed no correlation with serum levels of DDT. More recently cognitive functions of Indian DDT sprayers have been tested. DDT levels were 8.5 times higher than those in controls and visuomotor functions were significantly depressed (Misra *et al.*, 1984).

Laws *et al.* (1973) made a detailed study of the liver function of 31 men who had made and formulated DDT and who had been the subjects of an earlier study already discussed. Judging from their excretion and storage, the men's exposure was equivalent to an oral intake of DDT at rates ranging from 3.6 to 18 mg/man/day for periods ranging from 16 to 25 years and

averaging 21 years. All tests were in the normal range for total protein, albumin, total bilirubin, thymol turbidity, and retention of sulfobromophthalein sodium (BSP). One man had mild elevation of alkaline phosphatase (16 units) and SGPT (42 units). Another man had an alkaline phosphatase concentration of 14 units, while a third man had an SGPT level of 49 units. The α -fetoprotein test was negative for all 20 of the men for whom the test was performed.

The induction by DDT of microsomal enzymes of human liver was demonstrated first in workers, and it has been confirmed (see Section 7.4.3 and Therapeutic Use in this section). DDT may be more important than DDE in this regard, as indicated by the fact that Poland *et al.* (1970) observed induction in men with average serum levels of 0.573 and 0.506 ppm for DDT and DDE, respectively, while Morgan and Roan (1974) found no induction in men with corresponding values of 0.052 and 0.222 ppm.

As noted under Therapeutic Use, DDT has been used successfully to induce microsomal enzymes in order to promote metabolism of bilirubin in a case of congenital defect and to promote metabolism of phenobarbital in a case of overdose.

DDT promotes its own metabolism in some species of laboratory animals. That the same is true in humans is indicated by the fact that storage of DDT is relatively less at higher dosages (see Fig. 7.4). However, the metabolism and subsequent excretion of DDT can be promoted even more by phenobarbital and especially diphenylhydantoin (see Metabolism in Section 15.3.1.2) and to a lesser degree by some other drugs (McQueen *et al.*, 1972). Establishment of a reduced equilibrium appeared to require about 2 months. Within this period, the regression of the level of DDT plus DDE on duration of treatment with diphenylhydantoin was highly significant ($P < 0.001$).

In addition to the studies already mentioned regarding workers with extensive storage and/or excretion of DDT as a result of truly heavy exposure to DDT, studies also have been made of a larger number of workers with lesser storage and/or excretion following lesser exposure to DDT but greater exposure to other insecticides. Continuing, meticulous study discussed by Hayes (1975) under Community Studies as well as the work of Tsutsui *et al.* (1974), Ouw and Shandar (1974), and Morgan and Lin (1978) has failed to reveal effects of clinical significance among workers with prolonged, moderate exposure to a wide variety of pesticides. In a review of results for 2620 persons exposed to pesticides and 1049 persons not occupationally exposed, Morgan and Lin (1978) found that, apart from serum pesticide concentrations, the only significant and consistent change associated with occupational exposure was a depression of serum bilirubin. This presumably was a reflection of a slight induction of liver microsomal enzymes. In addition, there was a tendency for serum alkaline phosphatase, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), and lactate dehydrogenase (LDH) to increase with increasing concentrations of DDT plus DDE in the serum, but the differences were small in all instances and statistically significant for SGOT and LDH only.

Wong *et al.* (1984) could find no significant overall cause-specific mortality excess among men potentially exposed at work to DDT from 1935 to 1976. Similarly, a population of 499 persons living downstream from a defunct DDT-manufacturing plant showed no DDT-specific illnesses or ill health despite total DDT serum levels three times the national mean (Kreiss *et al.*, 1981). There was, however, a possible association between serum DDT and serum cholesterol, triglyceride, and γ -glutamyl transpeptidase levels.

A positive linear correlation has been reported for the concentrations of vitamin A and of DDT-related compounds in the serum of men with at least 5 years of occupational exposure to DDT. However, the workers' DDT levels were little higher than those of persons in the general population (see Table 7.15 in Hayes, 1975, and Table 15.11, herein), and their vitamin A levels were within normal limits (Keil *et al.*, 1972b). Perhaps they were better fed than the controls.

Evidence regarding mutagenic activity of DDT and its significance in humans is uncertain. Comparing samples collected in winter and during the peak season of pesticide application, a slight increase in chromatid breaks was reported in the cultured lymphocytes of workers exposed to a wide variety of insecticides said to include DDT. A somewhat larger increase was reported for men exposed mainly to herbicides (Yoder *et al.*, 1973). The paper failed to explain why exposure to DDT was claimed at a time when its use was banned. In another study, lymphocytes cultured from workers with an average DDT plasma level of 0.999 ppm showed significantly more chromosomal and chromatid aberrations than did cells cultured from controls with an average plasma level of 0.275 ppm. The difference was not significant in other comparisons in which the average plasma levels were 1.030 versus 0.380 ppm and 0.240 versus 0.030 ppm, respectively (Rabello *et al.*, 1975). Examination of all of the data presented by the authors suggests that a simple dosage-effect relationship was present, with a detectable effect starting somewhere between 0.2 and 0.4 ppm and increasing at levels higher than 0.4 ppm. Some chromosomal aberrations have also been observed with human lymphocyte cultures by Preston *et al.* (1981), but DDT did not cause unscheduled DNA synthesis in SV40-transformed human cells (Ahmed *et al.*, 1977).

Although there is a lot of evidence against DDT's causing liver cancer in humans in Western countries, there is still the outside possibility of it acting as a promoter of potent carcinogens. Aflatoxin is a well-known human carcinogen in areas of Southeast Asia such as Thailand, where DDT and other chlorinated insecticides are still widely used. In Denmark, Unger and Olsen (1980) have found significantly higher levels of DDE in adipose tissue from terminal cancer patients than in tissue from patients who died from other causes. In the United States, DDT and DDE levels were measured in 919 subjects in 1974 and 1975. After 10 years there was no correlation between these levels and overall mortality or cancer mortality except a slight correlation with respiratory cancer death (Austin *et al.*, 1989). Of course, increased storage often correlates with emaciation of whatever cause (Hayes, 1975).

Atypical Cases of Various Origins It has been alleged that DDT causes or contributes to a wide variety of diseases of humans and animals not previously recognized as associated with any chemical. Such diseases included cardiovascular disease, cancer, atypical pneumonia, retrosternal fibroplasia, poliomyelitis, hepatitis, and "neuropsychiatric manifestations" (Biskind, 1952, 1953; Biskind and Bieber, 1949). Without exception, the causes of these diseases were unknown or at least unproved at the time of the allegation. Needless to say, the charge that DDT predisposed to poliomyelitis was dropped after the disease was controlled through the use of vaccines. Unfortunately, there is no immediate possibility of controlling cardiovascular disease, cancer, or many of the less common conditions in humans that have been ascribed to DDT. In the meantime, such irresponsible claims could produce great harm and, if taken seriously, even interfere with scientific search for true causes and realistic means of preventing the conditions in question.

"Highly sensitive subjects" were said to experience visual disturbances, headache, perceptual abnormalities, muscular weakness, and decrease in mental and physical activity when a food oil solution containing as little as 10 ppm DDT was held beneath their nostrils. Ordinary people could not distinguish the odor of solutions containing up to 10,000 ppm from that of plain oil, and they were unaffected (Kailin and Hastings, 1966). This finding is unconfirmed; if such highly sensitive subjects exist, they are excessively rare.

There is a strong tendency to blame blood dyscrasias, other manifestations of "hypersensitivity," and, in fact, many diseases of unknown cause on any new chemical that gains widespread attention. DDT was no exception. A review of the early literature (Hayes, 1959a) indicates that blood dyscrasias and an unbelievable range of other diseases were, in fact, blamed on DDT. Only a circumstantial relationship ever was established between these diseases and exposure to DDT, and this remains true of the small number of reports of blood dyscrasias (Schüttmann, 1968; Murray *et al.*, 1973) or angioneurotic edema (Vanat and Vanat, 1971) that appeared later. As the novelty wore off, fewer new reports appeared linking DDT to diseases of unknown cause, although the use of DDT increased greatly. It is true that available tests do not make it possible to exclude a particular compound as a cause of an isolated case of blood dyscrasia (see Section 8.1.4.1). However, it is noteworthy that the rate at which these disorders occur has remained essentially unchanged since before DDT was introduced (see Fig. 7.10 in Hayes, 1975).

Eight cases of chronic liver disease have been reported among men with prolonged occupational exposure to DDT and BHC in connection with either their manufacture or use (Schüttmann, 1968). The cases were well studied individually but not epidemiologically.

There are a few reports of acute illness among workers attributed to exposure to mixtures of DDT and other materials. Insofar as the dosage was very large, as in certain accidents that have occurred involving individuals or groups in the general population, one would expect similar results. However, in at

least one instance, headache, dizziness, nausea, vomiting, pain and numbness of the limbs, and general weakness beginning 1–1.5 hr after entering a treated field (Kolyada and Mikhal'chenkova, 1973) was suggestive of food poisoning or hysteria.

Finally, there are studies of workers exposed to DDT and various other pesticides that are reported to have produced a variety of subjective and even objective medical findings. Interpretation of these reports is difficult because (a) the findings do not resemble those of poisoned animals or of persons poisoned as a result of accident or suicide and (b) the papers fail to report how the medical findings and the absenteeism of the pesticide workers compared with those of workers of comparable age, sex, and exertion who were not exposed to chemicals. The fact that the workers in question were exposed to mixtures of pesticides is not in itself an explanation because many workers, on whom careful study revealed no consistent difference from the controls, were exposed to mixtures.

The reports under discussion tend to fall into two sets, those involving general debility and those involving a single organ or system. Conditions representative of general debility include dermatitis, subtle blood changes, general weakness, palpitations, functional angiospasm, headache, dizziness, diminished appetite, vomiting, lower abdominal pain, chronic gastritis, benign chronic hepatitis, insomnia, a sympathetic vascular/asthenic syndrome, vegetative dystonia, and confusion (Jovčić and Ivanuš, 1968; Model', 1968; Kostiuk and Mukhtarova, 1970; Bezuglyi *et al.*, 1973).

Organs, systems, or functions that have been studied apparently by specialists and to the complete exclusion of other organs, systems, or functions of the same workers include the respiratory system (Boiko and Krasnyuk, 1969), liver (Krasnyuk *et al.*, 1967; Bezuglyi and Kaskevich, 1969), stomach (Krasnyuk and Platonova, 1969; Platonova, 1970), kidneys (Krasnyuk *et al.*, 1968), labor and puerparium (Komarova, 1970; Nikitina, 1974), adrenals (Baksheyev, 1973), and skin (Karimov, 1969, 1970). An indication that the difficulties under discussion are not serious is their reversal or prophylaxis by means of diet. Leshchenko and Polonskaia (1969) described in detail two dietary supplements composed of ordinary foods plus sea kale and a selection of vitamins and trace metals. Organochlorine workers who received these diet products showed a normalization of protein metabolism manifested by an increase in total serum protein, improved lipid metabolism, and enriched vitamin and trace element supply in the organism. All of these effects led to an improvement of the detoxifying function of the liver, which was viewed as the most frequent site of adverse effects of exposure to organochlorine compounds. The frequency and degree of olfactory disorders, especially ability to detect peppermint and acetic acid in an olfactory analyzer, were reported to be greater among persons exposed to pesticides and increased with duration of exposure (Salikhodzhaev and Fershtat, 1972). Whether any of the persons exposed to pesticides experienced any clinical difficulty or social inconvenience associated with olfactory sensation is not clear.

Dosage Response The clinical effects of different dosage levels of DDT in humans are summarized in Tables 7.24 in Hayes (1975) and in Tables 15.8 and 15.10, herein. The degree of storage determined by different dosage levels of DDT has been summarized in Fig. 7.4, and details regarding higher than normal dosage rates are given in Table 15.9. A clinically useful degree of induction of microsomal enzymes was obtained with a DDT dosage of 1.5 mg/kg/day for 6 months (see paragraph on Therapeutic Use). As discussed under Use Experience and in Section 7.4.3, workers who absorbed a dosage of about 0.25 mg/kg/day showed demonstrable but only slight induction. Workers with less exposure as indicated by lower serum levels of DDT showed no detectable induction.

Storage in Fat The highest reported storage of DDT and related compounds remains that of a healthy worker whose fat contained DDT and DDE (as DDT) at concentrations of 648 and 483 ppm, respectively (Hayes *et al.*, 1956). Laws *et al.* (1967) reported considerably lower storage values among the most exposed persons in a DDT manufacturing plant (see Table 15.11). An important point evident from the table is that, whereas almost all investigations of workers are said to have been carried out on "heavily exposed" populations (or words to that effect), some of the groups studied had absorbed little more DDT than is absorbed by the general population—especially the general population of some tropical countries—as recorded in Table 15.12.

The first evidence that human beings metabolize a part of the DDT they absorb to DDE was obtained from the analysis of fat from a worker (Mattson *et al.*, 1953). The accumulation of DDE relative to total DDT-related compounds is best illustrated in humans. Of the total DDT stored in the fat of workers exposed to technical DDT (about 4% DDE) for 11–19 years, only 38% was in the form of DDE, and, of course, some of that DDE came from their diets including meat (Laws *et al.*, 1967). In India, where many people avoid meat but may consume milk, cheese, and eggs, 34–41% of total DDT stored by people without special exposure was DDE (Dale *et al.*, 1965). In the United States, during a time when DDT residues in food were decreasing, the proportion of total DDT in the form of DDE increased from about 60% in 1955 to about 80% in 1970; during the same interval the concentration of total DDT in body fat decreased from about 15 ppm to less than 10 ppm as recorded in Table 7.10 in Hayes (1975). By 1980, DDE constituted 86.7% of total DDT in one population (Kreiss *et al.*, 1981). Thus, a low proportion of DDE indicates a relatively high intake of performed DDT and relatively few years for metabolism of stored DDT to DDE.

A number of factors, especially dosage, age, sex, race, and various disease states, have been discussed in connection with the storage and excretion of DDT by people (see Section 7.2.3), but only dosage has been shown to be of practical importance.

DDT and related compounds are stored at much lower rates in the general population than in persons with occupational exposure. However, these relatively low levels of storage constitute one of the most important aspects of the measurable

effects of pesticides on people. Consequently, these values have been presented and discussed in detail (see Section 7.2.2.2 and Table 15.12). Briefly, storage of total DDT in the body fat of ordinary people in the United States increased from 5.3 ppm in 1950 to about 15.6 ppm in 1955 and 1956. Thereafter, the levels decreased gradually, albeit somewhat irregularly, to about 8 ppm in 1970 and to 3 ppm in 1980 (see Fig. 7.3). In annual surveys in the United States based on 898–1920 samples per year, the geometric mean levels for total DDT in adipose tissue on a lipid basis were 7.88, 7.95, 6.88, 5.89, and 5.02 ppm for fiscal years 1970, 1971, 1972, 1973, and 1974, respectively. For each year, the values were higher for older age groups and higher for black than for white people. During fiscal year 1974, the values for persons 0–14, 15–44, and 45 years old or more were 2.15, 4.91, and 6.55 ppm, respectively, for white people and 4.02, 9.18, and 11.91 ppm, respectively, for black people (Kutz *et al.*, 1977). The values would have been somewhat lower if they had been based on wet weight.

It has been calculated that if exposure to DDT ceased it would take 10–20 years for DDT to disappear from a person but that DDE would persist throughout the life span (Morgan and Roan, 1977).

Storage in Blood No information is available on blood levels of DDT in persons poisoned by the compound. Concentrations measured in the blood or serum of workers are shown in Table 15.11. The highest value for total DDT in serum reported from several countries was 2.2017 ppm (with an average of 0.7371 ppm) based on gas chromatography (Laws *et al.*, 1967). A different situation is indicated by a report by Genina *et al.* (1969), who used a total chloride method to analyze samples of blood from controls and from persons with occupational exposure to DDT, polychloropinene, and BHC. These authors reported chlororganic compounds as high as 38.4 ppm in the blood of warehousemen. This concentration is about 20 times the highest value found by the same authors in their control group. The factor of 20 is not remarkable, but (especially in view of the fact that polychloropinene and BHC are excreted more readily than DDT and DDE) values as high as 9 ppm in the controls are completely unexpected. Whether the difference was based on massive exposure or analytical factors is unclear.

The concentrations of DDT in the blood of ordinary people are shown in Table 15.13 and are discussed in Section 7.2.3. It is of interest that although each person without special exposure to DDT has relatively constant serum levels of DDT and DDE, and DDE values differ more than the DDT values from person to person (Apple *et al.*, 1970). Whether this reflects differences in metabolism or differences in past exposure is unclear. Kreiss *et al.* (1981) have shown that DDE in serum samples of a community exceptionally exposed to DDT increased with age of the individual.

Surveys have demonstrated a gradual decline in the concentrations of DDT and related compounds in human fat. Presumably a similar decline has occurred in the levels of these compounds in human serum, but apparently no surveys have been carried out and, therefore, no direct evidence is available.

When storage of DDT has been found to be greater in black

Table 15.12

Concentrations of Some Chlorinated Hydrocarbon Pesticides in Body Fat of the General Population of Different Countries

Country	Year	Number of samples	Total DDT (ppm)	Total BHC (ppm)	Dieldrin (ppm)	Heptachlor epoxide (ppm)	References
North America							
Canada	1959-1960	62	4.9				Read and McKinley (1961)
	1966	47	4.39				Brown (1967)
	1966	35			0.22		Brown (1967)
	1966	42		0.07			Brown (1967)
	1966	22				0.14	Brown (1967)
	1967-1968	51	5.86				Kadis <i>et al.</i> (1970)
	1969	221	4.85	0.015	0.122	0.040	Ritchey <i>et al.</i> (1973)
	unknown				≤1.810	≤0.518	Larsen <i>et al.</i> (1971)
	unknown				≤0.087	≤0.136	Larsen <i>et al.</i> (1971)
	unknown		5.83				Brown and Chow (1975)
	1972	168	2.57	0.65	0.069	0.043	Mes <i>et al.</i> (1977)
	1976	99	2.06	0.158	0.049	0.037	Mes <i>et al.</i> (1982)
	1979-1981	91	3.78		0.036	0.035	Williams <i>et al.</i> (1984)
Greenland	1974	33	3.3		0.09	0.12	Jensen and Clausen (1979)
United States	<1942	10	ND ^a				Hayes <i>et al.</i> (1958)
	1950	75	5.3				Laug <i>et al.</i> (1951)
	1955	49	19.9				Hayes <i>et al.</i> (1956)
	1954-1956	61	11.7				Hayes <i>et al.</i> (1958)
	1956	36	15.6				Hayes <i>et al.</i> (1971)
	1961-1962	130	12.7				Quinby <i>et al.</i> (1965a)
	1961-1962	28	6.7	0.20	0.15		Dale and Quinby (1963)
	1962-1963	282	11.1	0.57	0.11		Hoffman <i>et al.</i> (1964)
	1964	64	7.6		0.31	0.10	Zavon <i>et al.</i> (1965)
	1964	25	10.3	0.60	0.29	0.24	Hayes <i>et al.</i> (1965)
	1964-1965	18	9.0		0.002-0.8		Schafer and Campbell (1966)
							Radomski <i>et al.</i> (1968)
(Florida)	1964-1965	42	10.6		0.215		Fiserova-Bergerova <i>et al.</i> (1967)
	1964-1965	42					Hoffman <i>et al.</i> (1967)
(Chicago)	1962-1966	221-994 ^b	10.4	0.48	0.14	0.16	Davies <i>et al.</i> (1968)
	1964-1965	12	11.5				Davies <i>et al.</i> (1968)
	1965-1967	17	5.5				Davies <i>et al.</i> (1968)
	1965-1967	90	8.4				Davies <i>et al.</i> (1968)
	1965-1967	17	7.8		0.0300	0.0220	Casarett <i>et al.</i> (1968)
(Hawaii)	1965-1967	30	6.51		0.630	0.0320	Casarett <i>et al.</i> (1968)
(Hawaii)	1965-1967	29	6.31		0.0270	0.0270	Casarett <i>et al.</i> (1968)
(Hawaii)	1965-1967	30	6.17		0.22		Edmundson <i>et al.</i> (1968)
	1965-1967	146			0.21		Radomski <i>et al.</i> (1968)
	1965-1967	42			0.15	0.05	A. Yobs, personal communication (1969)
(11 states)	1965-1967	733	6.22	0.29	0.10	0.05	A. Yobs, personal communication (1969)
(20 states)	1965-1967	3104	7.67	0.24	0.14		Morgan and Roan (1970)
(Arizona)	1966-1968	70	6.69				Warnick and Carter (1972)
	1967-1971	103	7.1				Wyllie <i>et al.</i> (1972)
(Idaho)	1970	200	9.9	0.3	0.2	0.1	Kutz <i>et al.</i> (1974b)
	1970	1412	7.87 ^{c,d}	0.43 ^{c,d}	0.18 ^{c,d}	0.09 ^{c,d}	Burns (1974)
(Texas)	1969-1972	221	23.18	1.29	0.35		Kutz <i>et al.</i> (1977)
	1970	1410	7.88 ^d				Kutz <i>et al.</i> (1977)
	1971	1612	7.95 ^d				Kutz <i>et al.</i> (1977)
	1972	1919	6.88 ^d				Kutz <i>et al.</i> (1977)
	1973	1092	5.89 ^d		0.30 ^d		Domanski <i>et al.</i> (1977)
(Pennsylvania, black)	1973-1974	14	14.0 ^d		0.24 ^d		Domanski <i>et al.</i> (1977)
(Pennsylvania, white)	1973-1974	13	5.1 ^d				Kutz <i>et al.</i> (1977)
	1974	898	5.02 ^d		0.17	0.16	Greer <i>et al.</i> (1980)
(Louisiana)	1977	22	8.29		0.15	0.06	Barquet <i>et al.</i> (1981)
(Florida)	unknown	10	6.71				

(continued)

Table 15.12 (Continued)

Country	Year	Number of samples	Total DDT (ppm)	Total BHC (ppm)	Dieldrin (ppm)	Heptachlor epoxide (ppm)	References
Central America and Mexico							
Costa Rica	1984?	30	59.2 ^d		0.16 ^d	0.38 ^d	Barquero and Constenla (1986)
Mexico	1975	19	21.47 ^d		0.06 ^d		Albert <i>et al.</i> (1980)
South America							
Argentina	1967	37	13.2	2.44	0.38	0.192	Wassermann <i>et al.</i> (1968a)
Venezuela	1964	38	10.3	0.16	0.60		W. E. Dale, personal communication (1971)
Brazil	1969–1970	38	4.1				Wassermann <i>et al.</i> (1972c)
Europe							
Austria	1966		6.33	1.9	0.1		Pesendorfer <i>et al.</i> (1973)
Belgium	1964	20	3.3				Maes and Heyndrickx (1966)
	1975	60	8.29	0.76	0.26	0.38	Djonckheere <i>et al.</i> (1977)
Czechoslovakia	1963–1964	229	9.6				Halacka <i>et al.</i> (1965)
	1975–1976	13	2.26–3.97	2.55–20.95			Dubsky <i>et al.</i> (1977)
Denmark	1965	18	3.3		0.20		Weihe (1966)
	1974	17	1.8		0.09	0.08	Jensen and Clausen (1979)
England	1961–1962	131	2.2		0.21		Hunter <i>et al.</i> (1963)
	1963–1964	66	3.3	0.42	0.26	0.1	Egan <i>et al.</i> (1965)
	1964	100	3.9	0.02	0.21	0.1	Robinson <i>et al.</i> (1965)
	1964	44	4.0		0.22		Robinson and Hunter (1966)
	1965	101	2.85	0.19	0.34		Cassidy <i>et al.</i> (1967)
United Kingdom	1965–1967	248	3.00	0.31	0.21	0.04	Abbott <i>et al.</i> (1968)
	1969–1971	201	2.5	0.29	0.16	0.03	Abbott <i>et al.</i> (1972)
	1976–1977	236	2.6	0.33	0.11	0.03	Abbott <i>et al.</i> (1981)
	1982–1983	187	1.54	0.30	0.08		Abbott <i>et al.</i> (1985)
Finland	1972–1974	73	2.5				Hattula <i>et al.</i> (1976)
	1983	65	0.33			0.002	Mussalo-Rauhama <i>et al.</i> (1984)
France	1961	10	5.2	1.19			Hayes <i>et al.</i> (1963)
Germany (East)	1966–1967	100	13.1	0.16			Engst <i>et al.</i> (1967)
	1958–1959	60	2.3				Maier-Bode (1960)
Germany (West)	1970	20	3.6	0.45			Acker and Schulte (1970)
			3.8	0.5	0.2		Acker and Schulte (1971)
		10	4.24	2.9	0.11	0.097	Acker and Schulte (1974)
		10	4.77	8.2	0.17	.12	Acker and Schulte (1974)
		10	5.42	5.9	0.091	0.062	Acker and Schulte (1974)
		10	8.36	4.8	0.082	0.085	Acker and Schulte (1974)
		10	7.80	6.4	0.23	0.096	Acker and Schulte (1974)
(workers)	1979?	8		54.5 ^d			Baumann <i>et al.</i> (1980)
Hungary	1960	48	12.4				Denes (1962)
	1964	15			0.16		Denes (1966)
	1969		13.7	2.30			Berend <i>et al.</i> (1970)
	1970		18.9	0.76			Soos <i>et al.</i> (1972)
Italy	1965	9	5.0		0.594		Kanitz and Castello (1966)
	1965–1966	18	10.86	2.25	0.84	0.46	Paccagnella <i>et al.</i> (1967)
	1966	22	15.48	0.08	0.68	0.23	Del Vecchio and Leoni (1967)
	1970?	31	16.75	0.02	0.10		Prati and Del Dot (1971)
Netherlands	1983–1984	26	8.99 ^e				Focardi <i>et al.</i> (1986)
	1964	20	7.7				Wit (1964)
	1966	11	2.22	0.11	0.20	0.01	De Vlieger <i>et al.</i> (1968)
Norway	1972	7	10				Bjerk (1972)
	1975–1976	58	0.75–2.60				Kveseth <i>et al.</i> (1979)
	1981–1982	16	0.448				Brevik and Bjerk (1978)
							Skaare <i>et al.</i> (1988)

(continued)

Table 15.12 (Continued)

Country	Year	Number of samples	Total DDT (ppm)	Total BHC (ppm)	Dieldrin (ppm)	Heptachlor epoxide (ppm)	References
Poland	1965	72	13.4				Bronisz <i>et al.</i> (1967)
	1970	70	11.4	0.5	ND		Juskiewicz and Stec (1971)
	1972	15	5.23				Bojanowska <i>et al.</i> (1973)
	1977-1978	100	4.47	0.216			Syrowatka <i>et al.</i> (1979)
Romania		20		0.48-42			Mandroiu and Iordachescu (1971)
	1972-1973		2.41				Ciupe (1976)
Spain	1966	41	15.7				Llinares and Wasserman (1968)
	1970s	40	4.549	0.062	0.15	0.015	Herrea-Martache <i>et al.</i> (1978)
	1980s	55	8.95	1.38	0.27	0.16	To-Figueras <i>et al.</i> (1986)
Switzerland		12	1.9-16.3	0.3-1.8	0.07-0.57		Zimmerli and Marek (1973)
		41	8.06				Vas'Kovskaja and Komarova (1963)
USSR		197	8.8658-15.4794	2.15			Vas'Kovskaja (1969)
Africa							
	Nigeria	43	8.8				Wassermann <i>et al.</i> (1968b)
	1969	41	6.5	0.19			Wassermann <i>et al.</i> (1972c)
Kenya		83	5.4		0.1	0.1	Wassermann <i>et al.</i> (1972b)
South Africa (Bantu)	1969	73	5.94	1.93	0.034	0.01	M. Wassermann <i>et al.</i> (1970b)
		41	7.16	3.27	0.047	0.01	M. Wassermann <i>et al.</i> (1970b)
		75	2.9	0.1		0.02	Wassermann <i>et al.</i> (1974a)
Uganda							
Asia							
	Burma	43	0.3-7.0				Shure and Law (1977)
	India	35-67	26	1.43	0.04		Dale <i>et al.</i> (1965)
	1964	16	13				Dale <i>et al.</i> (1965)
	unknown	94	21.8				Ramachandran <i>et al.</i> (1973)
Iran							Mukherjee <i>et al.</i> (1980)
	1975-1976	100	0.45				Kaphalia and Seth (1983)
	1981?	6	1.754	2.344			Bhaskaran <i>et al.</i> (1979)
	1976	14	4.7				Hashemy-Tonkabony and Soleimani-Amin (1978)
Israel	1974-1976	170	8.13	0.26	0.049		Wassermann <i>et al.</i> (1965)
							Wassermann <i>et al.</i> (1967)
Japan	1963-1964	254	19.2				Wassermann <i>et al.</i> (1967)
	1965-1966	71	4.6				Wassermann <i>et al.</i> (1967)
	1965-1966	133	8.2				Wassermann <i>et al.</i> (1974b)
	1967-1971	63	14.4				Curley <i>et al.</i> (1970)
	1968-1969	241	2.4	0.12-1.28	0.13	0.02	Nishimoto <i>et al.</i> (1970)
	1969-1970	74	6.92	12.17	0.46	0.01	Doguchi <i>et al.</i> (1971)
	1970	21	3.69		0.33		Suzuki <i>et al.</i> (1973)
	1970		4.499	2.420	0.163		Suzuki <i>et al.</i> (1973)
	1971		2.694	3.001	0.208		Kasai <i>et al.</i> (1972)
	1971	30	12.859	6.160	0.098		Suzuki <i>et al.</i> (1973)
	1972		4.001	3.698	0.429		Kasai <i>et al.</i> (1972)
	1972	42	5.992		0.310		Kawanishi <i>et al.</i> (1973)
Pakistan	1973	60	6.44	2.659	0.129		Inoue <i>et al.</i> (1974)
	1974	17	6.87	3.0			Fukano and Doguchi (1977)
	1974	30	3.59	2.36			Mori <i>et al.</i> (1983)
							Mori <i>et al.</i> (1983)
	1974	20	9.25 ^d	11.90 ^d			Mori <i>et al.</i> (1983)
	1976	22	4.79 ^d	4.92 ^d			Mori <i>et al.</i> (1983)
	1981	46	4.04 ^d	3.77 ^d			Mughal and Rahman (1973)
Pakistan		60	25.0	0.48	0.47		

(continued)

Table 15.12 (Continued)

Country	Year	Number of samples	Total DDT (ppm)	Total BHC (ppm)	Dieldrin (ppm)	Heptachlor epoxide (ppm)	References
Thailand	1969-1970	77	12.6	0.2	0.2		Wassermann <i>et al.</i> (1972c)
Turkey	1984-1985	48	7.12 ^d	1.72 ^d			Karakaya <i>et al.</i> (1987)
Oceania							
Australia	1965	53	1.81		0.05		Bick (1967)
	1965-1966	46	10.2				Wassermann <i>et al.</i> (1968a)
	1965-1966	12	10.5	0.68	0.67	0.02	Wassermann <i>et al.</i> (1968a)
	1971	75	4.94		0.21		Brady and Siyali (1972)
	1985-1986	292	3.72		0.13		Ahmad <i>et al.</i> (1988)
New Zealand	1963-1964	45		0.49			Dacre (1969)
	1966	52	5.8		0.27		Brewton and McGrath (1967)
	1965-1969	254	14.6		0.35		Copplestone <i>et al.</i> (1973)

^a Not detected.^b Different numbers of samples examined for different compounds.^c Geometric mean.^d Lipid basis.^e Dry weight basis.

people, the difference could be accounted for by greater exposure (Hayes, 1975; D'Ercole *et al.*, 1976). However, Sandifer (1974), who found that the concentrations of DDT in the sera of blacks was two to three times greater than those in whites, also found a significant correlation between total DDT and deficiency of glucose-6-phosphate dehydrogenase, a condition much more common in blacks than whites. Thus, a genetic factor in the storage of DDT appears possible, but additional evidence would be necessary to confirm it.

Whether the high storage in blacks is strictly environmental or partly genetic, it is certain that as high or higher levels have been recorded among several groups of rural blacks in different parts of the southeastern United States than were reported by Kreiss *et al.* (1981) among blacks in Triana, Alabama, who had mean values of 0.096 and 0.062 ppm for total DDT in the serum of males and females, respectively. Other average values for rural blacks have included 0.101 ppm for women (D'Ercole *et al.*, 1976), 0.072 and 0.066 ppm for children and mothers, respectively (Keil *et al.*, 1972a,b, 1973), 0.065-0.214 ppm for blacks of different ages or rural locations (Arthur, 1976), and 0.108 and 0.105 ppm for males and females in four rural communities in the Mississippi Delta (unpublished result from CDC). Thus, there is no evidence that DDT and related compounds downstream from a former DDT factory led to greater absorption than occurred in other places.

Storage in Other Tissues With the exception of concentrations of 19-36 ppm in heart, kidney, and liver of a man who died of DDT poisoning under unstated circumstances (Luis, 1952), no information is available on tissue levels in people with heavy exposure, whether occupational or otherwise. Storage of DDT and related compounds in the organs of adults and fetuses in the general population was discussed and tabulated

by Hayes (1975). Concentrations in the viscera of adults averaged 1.0 ppm, but concentrations in lymph nodes and especially bone marrow (a fatty tissue) approached the level in adipose tissue (≤ 6.0). Concentrations in some viscera of still-born infants were similar to those in adipose tissue of the same infants and also in adults, suggesting that there had been a mobilization of DDT from fat prior to death.

Saxena *et al.* (1987a) have reported that the levels of DDT in human leiomyomatous uterine tissue were much higher than those in normal tissue (means of 0.845 ppm and 0.103 ppm, respectively). Whether this is related to any estrogenic actions of DDT is unknown.

Secretion in Milk No information is available on the secretion of DDT in the milk of women who were occupationally exposed to the compound or who were made ill by it, regardless of circumstances. The concentrations of DDT in the milk of women in various general populations are shown in Table 15.14. As may be seen, values reported from Guatemala and early values from the USSR were much higher than those from other countries, and yet there was no indication of illness among babies fed such milk. The significance of DDT in milk and the dosages that different concentrations of it determine were discussed by Hayes (1975), Jensen (1983), Spindler (1983), and Coulston (1985).

Quinby *et al.* (1965a,b) noted that women apparently were in negative DDT balance during lactation, but no direct measurement of DDT intake of women participating in the study was made. More recently, the ingestion of DDT in food and the secretion of DDT in milk were measured in the same women, and the fact of negative balance was confirmed (Adamovic and Sokic, 1973; Adamovic *et al.*, 1978; Cocișiu *et al.*, 1976). In fact, it has been suggested that this phenomenon may be a

Table 15.13

Concentrations of Some Chlorinated Hydrocarbon Pesticides in Blood of the General Population of Different Countries

Country	Year	Number of samples	Total DDT (ppm)	Total BHC (ppm)	Dieldrin (ppm)	Heptachlor epoxide (ppm)	References
North America							
Canada			0.032				Brown and Chow (1975)
United States	1965	10	0.0418	0.0034	0.0019	0.0011	Dale <i>et al.</i> (1966a)
USA	1966	10, F ^a	0.0360				Dale <i>et al.</i> (1967)
	1966	10, M ^a	0.0746				Dale <i>et al.</i> (1967)
	1966–1967	53 ^b	0.00501	0.00048	0.00026	0.00021	Selby <i>et al.</i> (1969)
	1967	64	0.01425	0.00150	0.00069	0.00000	A. Yobs, personal communication (1969)
	1968	106	0.01397	0.00000	0.00014	0.00000	A. Yobs, personal communication (1969)
	1967–1986	1000	0.0294	0.0021	0.0005	0.00007	Watson <i>et al.</i> (1970)
(rural black)	1968	139	0.0109		0.0002		Finklea <i>et al.</i> (1972)
(urban black)	1968	175	0.0125		0.0002		Finklea <i>et al.</i> (1972)
(rural white)	1968	210	0.0056		0.0004		Finklea <i>et al.</i> (1972)
(urban white)	1968	199	0.0047		0.0003		Finklea <i>et al.</i> (1972)
	1969	30 ^{c,d}	0.0144	0.0030	0.0007	0.0011	Curley <i>et al.</i> (1969)
	1968	5 ^e	0.0050	0.0012	0.0009	0.0008	Curley and Kimbrough (1969)
	1968	10 ^e	0.0205	0.0034	0.0003	0.0006	Curley and Kimbrough (1969)
	1970	26	0.03169		0.00149		Radomski <i>et al.</i> (1971)
	1972	214 ^f	0.006–0.822	0.001–0.017	0.001–0.025		Griffith and Blanke (1975)
	1970s	33, F	0–0.0782	0–0.0058	0.001		Barquet <i>et al.</i> (1981)
(Alaska)	1972	38 ^j	0.002		0.011		Serat <i>et al.</i> (1977)
(urban)	1968–1970	275, M	0.0314		0.0003		Bloomer <i>et al.</i> (1977)
(urban)	1968–1970	205, F	0.0232		0.00015		Bloomer <i>et al.</i> (1977)
(rural)	1968–1970	232, M	0.0357		0.0003		Bloomer <i>et al.</i> (1977)
(rural)	1968–1970	243, F	0.0261		0.00011		Bloomer <i>et al.</i> (1977)
(black) ^d	1972–1973	209	0.007–0.292	0–0.009	0–0.003	0–0.003	D'Ercole <i>et al.</i> (1976)
(black) ^e	1972–1973	209	0.016–0.303	0–0.019	0–0.003	0–0.001	D'Ercole <i>et al.</i> (1976)
(white) ^d	1972–1973	130	0.003–0.056	0–0.009	0–0.002	0–0.002	D'Ercole <i>et al.</i> (1976)
(white) ^e	1972–1973	130	0.007–0.160	0–0.009	0–0.006	0–0.002	D'Ercole <i>et al.</i> (1976)
	1976–1980	3127	0.090	0.0002	0.0001		HANES II (1980)
(South Carolina)	1978	25			0–0.0034		Sandifer <i>et al.</i> (1981)
(Hawaii)	1979	200	0.004–0.152	0–0.0002	0–0.002		Takahashi and Parks (1982)
	1980	499	0.001–2.821				Kreiss <i>et al.</i> (1981)
South America							
Argentina	1970	20 ^g	0.01934	0.02399	0.00143		Radomski <i>et al.</i> (1971)
	1970	18 ^h	0.01327	0.00704	0.00094		Radomski <i>et al.</i> (1971)
	1970	19 ⁱ	0.00869	0.00704	0.00054		Radomski <i>et al.</i> (1971)
Brazil	1975	32, F	0.036				Prochanoy and Schwartsman (1982)
	1975?	32 ^d	0.0153				Prochanoy and Schwartsman (1982)
(industrial)	1980?	21	0.0219	0.0090			de Fornicola and de Azevedo (1982)
(rural)	1980?	21	0.0316	0.0087			de Fornicola and de Azevedo (1982)
Europe							
Hungary	1967–1968	120	0.034	0.019	0.001		Czegledi-Janko (1969)
Norway	1981–1982	15 ^e	0.019	0.001			Skaare <i>et al.</i> (1988)
(immigrants)	1981–1982	5 ^e	0.150	0.002			Skaare <i>et al.</i> (1988)
Poland			0.172, F	0.008, F			Jonczyk (1970)
	1972	15	0.030	0.084			Bojanowska <i>et al.</i> (1973)
	1979	100	0.0281	0.0092			Syrowatka <i>et al.</i> (1979)
		13	0.0209	0.0038			Zimmerli and Marek (1973)
Switzerland					0.0014		Reiner <i>et al.</i> (1977)
Yugoslavia	1975	147	0.07478	0.00734			Krauthacker <i>et al.</i> (1980b)
(urban)	1978–1979	11	0.0353				Krauthacker <i>et al.</i> (1980a)
(rural)	1979	41	0.0102				Roncevic <i>et al.</i> (1987)
	1980s	14, F	0.0162	0.0035			Bazulic <i>et al.</i> (1984)
	1978–1981	31, F	0.0215	0.0059			

(continued)

Table 15.13 (Continued)

Country	Year	Number of samples	Total DDT (ppm)	Total BHC (ppm)	Dieldrin (ppm)	Heptachlor epoxide (ppm)	References
Africa							
Tunisia	1980s	20	0.091	0.007			Jemma <i>et al.</i> (1986)
Asia							
India							
(Delhi)	1985?	50	0.301				Saxena <i>et al.</i> (1987b)
(Lucknow)	1981?	48, M	0.028	0.075			Kaphalia and Seth (1983)
(Lucknow)	1979-1980	29 ^e	0.026	0.0499			Saxena <i>et al.</i> (1983)
(Lucknow)	1970s	25 ^e	0.020	0.022			Siddiqui <i>et al.</i> (1981)
Israel	1975	19	0.0740	0.0147	0.0099	0.0136	Polishuk <i>et al.</i> (1977)
	1984-1985	14, M	0.0249		0.0027	0.0116	Pines <i>et al.</i> (1987)
Japan	1970	10	0.074	0.150			Tokutsu <i>et al.</i> (1970)
	1971		0.005	0.006	0.001		Kojima <i>et al.</i> (1971)
	1971	138	0.0183				Kasai <i>et al.</i> (1972)
			0.0093	0.191	0.0030		Yamagishi <i>et al.</i> (1972a)
	1971		0.0285	0.0577			Kaku (1973)
	1972		0.001-0.078	0.030-0.067	0.003		Study Group (1972)
		37	0.0437, F	0.030-0.046	0-0.0031		Nawa (1973)
		^e	0.1358	0.0326			Hara <i>et al.</i> (1973)
		^d	0.0210	0.0185			Hara <i>et al.</i> (1973)
		17		0.0118			Inoue <i>et al.</i> (1974)
Oceania	1973	82	0.0179	0.0106	0.0011		Abe <i>et al.</i> (1974)
Australia		52	0.0172	0.0032	0.0023	0.0031	Siyali (1972)
		47	0.0167				Ouw and Shandar (1974)

^a F, Female; M, male.^b Geometric mean.^c Mean of positive values only.^d Cord blood from live term infants.^e Maternal blood.^f Ages 41-60.^g Adults.^h 6-11 years old.ⁱ 1-5 years old.^j 6-17-year-old Eskimos.

significant factor in determining the lower levels of DDT found in women than men in the general population (Adamovic and Sokic, 1973).

Johnsson *et al.* (1977) found significantly lower levels of DDT (mean of 0.008 ppm) and of DDE (mean of 0.035 ppm) than had been reported earlier for the milk of city dwellers. However, levels remained quite high (0.05-1.90 ppm) in some rural black people (Woodard *et al.*, 1976). Some evidence suggests that DDT levels are higher in milk from smokers than nonsmokers, although there may be an occupational explanation (Coulston, 1985).

Overall, despite the presence of DDT in human milk and placenta, there seems little risk to neonates in many different populations.

Excretion of DDT-Related Compounds Among workers whose DDT intake was estimated to be about 35 mg/day, Ortelee (1958) reported that the concentration of DDA in urine ranged from 0.12 to 7.56 ppm and averaged 1.71 ppm. Among workers whose exposure was about half as great, Laws *et al.*

(1967) found concentrations from 0.01 to 2.67 ppm with a mean of 0.97 ppm.

Continuous sampling of a DDT-formulating plant worker's urine showed that excretion of DDA increased promptly when exposure began on each of 5 consecutive workdays but often continued after exposure, sometimes reached a peak about midnight, and then decreased rapidly. On day 6, when there was no occupational exposure to DDT, the excretion of DDA continued until a very low level was reached. The highest concentration of DDA reported in this study was 0.68 ppm (Wolfe and Armstrong, 1971).

The urine of people in the general population contains not only DDA but also neutral compounds; the average concentrations reported by Cueto and Biros (1967) were: *p,p'*-DDT, 0.0007 ppm and *p,p'*-DDE, 0.0156 pm. Men with heavy occupational exposure to DDT excreted much more DDA but showed only a statistically insignificant increase in excretion of DDT and DDE.

The values just given for the average excretion of DDA, DDT, and DDE by different, small groups of people would

Table 15.14

Concentrations of Some Chlorinated Hydrocarbon Pesticides in Milk of the General Population of Different Countries

Country	Year	Number of samples	Total DDT (ppm)	Total BHC (ppm)	Dieldrin (ppm)	Heptachlor epoxide (ppm)	References
North America							
Canada	1967-1968	147	0.139		0.005	0.003	Ritchey <i>et al.</i> (1972)
	unknown	15	0.019-0.035				Musial <i>et al.</i> (1974)
	unknown				0.009	0.003	Larsen <i>et al.</i> (1971)
	unknown				0.013	0.052	Larsen <i>et al.</i> (1971)
United States	1969-1974	101					
	1970	90	0.077	0.002	0.005	0.004	Mes <i>et al.</i> (1977)
	1975	100	0.046	0.002	0.002	0.001	Mes and Davies (1979)
	1978-1979	154	0.039				Dillon <i>et al.</i> (1981)
	1982	210	0.038	0.008	0.002		Collins <i>et al.</i> (1982)
	1986?	18	0.016	0.006	0.0004	0.0002	Davies and Mes (1987)
	1950	32	0.13				Laug <i>et al.</i> (1951)
	1960-1961	10	0.12				Quinby <i>et al.</i> (1965b)
	1962	6	0.37 ^a				West (1964)
	1968	unknown	0.078			0.0066	Curley and Kimbrough (1969)
	1970	53	0.101				Kroger (1972)
	1970-1971	101	0.17				Wilson <i>et al.</i> (1973)
	1975	55	0.114				Bradt and Herrenkohl (1976)
	1973-1974	57	0.344	0.005	0.004	0.004	Strassman and Kutz (1977)
	1971-1972	40	0.126				Savage <i>et al.</i> (1973)
(black)	1974	38	0.447				Woodard <i>et al.</i> (1976)
(white)	1974	14	0.075				Woodard <i>et al.</i> (1976)
(total)	1975	1436	0.070	0.003	0.002	0.001	Savage <i>et al.</i> (1981)
(pesticide workers)	1973-1975	34	0.719	0.022	0.006	0.003	Barnett <i>et al.</i> (1979)
(non-pesticide workers)	1973-1975	6	0.083	0.011	0.004	0.002	Barnett <i>et al.</i> (1979)
(Hawaii)	1979-1980	54	2.16 ^b	0.180 ^b	0.042 ^b	0.036 ^b	Takei <i>et al.</i> (1983)
(Missouri)	1977	51	0.022	0.003	0.014		Jonsson <i>et al.</i> (1977)
Central America and Mexico							
El Salvador	1973-1974	40	0.695	0.012	0.005	0.003	de Campos and Olszyna-Marzys (1978)
Guatemala							
(La Bomba)	1970	10	2.15	0.03	trace	0.003	Olszyna-Marzys <i>et al.</i> (1973)
(El Rosario)	1970	27	1.84	0.007	0.002	0.007	Olszyna-Marzys <i>et al.</i> (1973)
(Cerro Colorado)	1971	9	4.07	0.02			Olszyna-Marzys <i>et al.</i> (1973)
(City)	1974	15	0.480				de Campos and Olszyna-Marzys (1978)
(Izabal)	1974	10	2.55		0.005	0.002	de Campos and Olszyna-Marzys (1978)
(Escuintla)	1974	10	3.54		0.070	0.003	de Campos and Olszyna-Marzys (1978)
Mexico	1976	15	0.266		0.030		Albert <i>et al.</i> (1981)
South America							
Argentina	1981	20	0.061	0.037			Landoui and Astolfi (1982)
Chile	1977	unknown	0.258				Albert (1981)
Brazil	1975-1976	26	0.090				Matuo <i>et al.</i> (1980)
Uruguay		10	0.230	0.057	0.032	0.002	Bauza (1975)
Europe							
Austria							
(Vienna)		22	4.725 ^b	1.488 ^b			Pesendorfer (1975)
(Mistelbach)		9	6.13 ^b	4.013 ^b			Pesendorfer (1975)
Belgium	1968	20	0.128	0.010	0.004		Heyndrickx and Maes (1969)
	1982	47	0.041	0.0567		0.0021	Rogirst <i>et al.</i> (1983)
Czechoslovakia	1968	unknown	0.101				Hruska (1969)
		393	0.209				Suvak (1970)
Denmark	1982	57	1.15 ^b	0.08 ^b	0.04 ^b		Andersen and Orbaek (1982)
England	1963-1964	19	0.013	0.006			Egan <i>et al.</i> (1965)
United Kingdom	1979-1980	102	0.051	0.008	0.002		Collins <i>et al.</i> (1982)
Finland	1982	50	0.031				Wickström <i>et al.</i> (1983)

(continued)

Table 15.14 (Continued)

Country	Year	Number of samples	Total DDT (ppm)	Total BHC (ppm)	Dieldrin (ppm)	Heptachlor epoxide (ppm)	References
France		59 ^c		0–0.190	0.007–0.032	0.002–0.012	Luquet <i>et al.</i> (1972)
	1971–1972		3.24 ^b	2.75 ^b	0.23 ^b	0.28 ^b	Luquet <i>et al.</i> (1974a)
	1972–1973		3.51 ^b	1.77 ^b		0.28 ^b	Luquet <i>et al.</i> (1974b)
	1970	49		0.003–0.202	0.001	0.001	Goursaud <i>et al.</i> (1971)
	1974–1975	13	1.04 ^b	0.052 ^b	0.035 ^b	0.08 ^b	De Bellini <i>et al.</i> (1977)
Germany (West)	1970?	43	0.121				Acker and Shulte (1970)
Germany	1970?		0.569				Adamovic <i>et al.</i> (1971)
	1969	57	0.23				Engst and Knoll (1972)
	1970	18	0.16				Engst and Knoll (1972)
	1971	96	0.32				Knoll and Jayaraman (1973a,b)
	1970		4.1 ^b	0.54 ^b			Acker and Shulte (1971)
	1970						Acker and Shulte (1971)
	1973	184	0.23				Thielemann <i>et al.</i> (1975)
Germany (East)	1978	85	0.349				Thielemann (1979)
	1979	200	0.096	0.010			Hesse <i>et al.</i> (1981)
Germany (West)	1979–1980	unknown	2.00 ^b				Acker (1981)
Hungary	1963	10	0.13–0.26 ^d				Denes (1964)
Ireland	1971–1972		0.128 ^b	0.001 ^b	0.001 ^b	0.005 ^b	Downey <i>et al.</i> (1975)
Italy	1983–1985	65	0.051	0.007			Dommarco <i>et al.</i> (1987)
Netherlands	1969	50	2.7 ^b				Tuinstra (1971)
	1978?	69	0.031		0.0023		Eckenhausen <i>et al.</i> (1981)
Norway	1976	45	0.050				Brevik and Bjerk (1978)
	1979	19	0.024				Skaare (1981)
	1982	34	0.024	0.002			Skaare <i>et al.</i> (1988)
(immigrants)	1982	5	0.107	0.008			Skaare <i>et al.</i> (1988)
Poland		128	0.25	0.003			Juskiewicz <i>et al.</i> (1972)
	1966	26	0.27				Bronisz and Ochynski (1968)
	1967	25	0.40				Bronisz and Ochynski (1968)
	1970?	40	0.28	0.006			Kontek <i>et al.</i> (1971)
	1979	40	0.179				Kontek <i>et al.</i> (1981)
Portugal	1972	168	0.326				Graca <i>et al.</i> (1974)
Romania	1968?	100	0.08–1.58				Unterman and Sirghie (1969)
				0.08–1.58			Mandroui and Iordachescu (1971)
Spain	1979	45	0.181	0.039	0.0005		Pozo Lora <i>et al.</i> (1979)
	1981	20	0.256	0.020	0.003	0.004	Baluja <i>et al.</i> (1982)
Sweden	1967?	unknown	0.117				Lofroth (1968)
	1967–1969	22	0.115	traces	0.001		Westoo <i>et al.</i> (1970)
	1976–1977	?	0.033		0.0007		Westoo and Noren (1978)
	1978–1979	23	0.061	0.0036	0.0008		Hofvander <i>et al.</i> (1981)
USSR	1964	16	1.22–4.88				Damaskin (1965)
	1964–1965	4505	0.1–1.0				Gracheva (1969)
	1969?	680	0.25				Gracheva (1970)
	1967	370	0.1				Komarova (1970)
	1977?	252	0.580				Gulko <i>et al.</i> (1978)
Yugoslavia	1981–1982	50	0.0743	0.011			Krauthacker <i>et al.</i> (1986)
	1977	34	0.051				Krauthacker <i>et al.</i> (1980)
Africa							
Kenya							
(nomads)	1984	13	1.69 ^b	0.038 ^b	2.445 ^b		Kanja <i>et al.</i> (1986)
(farmers)	1985	48	9.76 ^b	0.22 ^b	0.310 ^b		Kanja <i>et al.</i> (1986)
Nigeria	1981–1982	35	1.51 ^b	0.52 ^b			Atuma and Vaz (1986)
Tunisia	1980s	80	0.145	0.039	0.006		Jamma <i>et al.</i> (1986)
Asia							
India							
(Lucknow)	1970s	25	0.12	0.107			Siddiqui <i>et al.</i> (1981)
(Punjab)	1979	75	0.51	0.195			Kalra and Chawla (1981)
(Bangalore)	unknown	6	0.053	0.014			Ramakrishnan <i>et al.</i> (1985)
(Calcutta)	unknown	6	0.114	0.031			Ramakrishnan <i>et al.</i> (1985)
(Bombay)	unknown	6	0.224	0.053			Ramakrishnan <i>et al.</i> (1985)
(Ahmedabad)	1981–1982	50	0.305	0.225			Jani <i>et al.</i> (1988)
Iran	1974–1976	131	0.044	0.008	0.011		Hashemy-Tonkabony and Fateminassab (1977)

(continued)

Table 15.14 (Continued)

Country	Year	Number of samples	Total DDT (ppm)	Total BHC (ppm)	Dieldrin (ppm)	Heptachlor epoxide (ppm)	References
Iraq	1983-1984	50	0.145	0.073	0.030		Al-Omar <i>et al.</i> (1985)
Israel	1975	29	0.0717	0.0101	0.0070	0.0091	Polishuk <i>et al.</i> (1977)
	1980s	100	0.0875	0.0125			Weisenberg <i>et al.</i> (1985)
Japan	1970-1971			0.02-0.4			Narafu (1971)
	1971-1972	398	0.0562				Anonymous (1972)
	1971	43	0.179				Hidaka <i>et al.</i> (1972)
	1970	10	0.071				Tokutsu <i>et al.</i> (1970)
	1970?	5	0.160				Takeshita and Inuyama (1970)
	1970?	10	0.120				Takeshita and Inuyama (1970)
	1971?		0.04				Kojima <i>et al.</i> (1971)
	1971?	59	0.019-0.105				Kato <i>et al.</i> (1971)
	1971?	14	0.047				Sugaya <i>et al.</i> (1971)
	1971	454	0.179	0.033-0.44			Hayashi (1972a,b); Study Group, 1972
	1971-1972	398	0.056				Anonymous (1972)
	1971		0.044				Yamagishi <i>et al.</i> (1972a)
		30	2.0 ^b				Mizoguchi <i>et al.</i> (1972)
		54	0.025				Taira <i>et al.</i> (1972)
	1971-1972	398	0.0626	0.105	0.0034	0.0011	Hayashi (1972a,b)
	1971-1972	5	0.027				Nagai (1972)
	1971-1972	5	0.037				Nagai (1972)
	1971-1972	5	0.016				Nagai (1972)
	1971-1972	5	0.037				Nagai (1972)
		30	0.033				Oura <i>et al.</i> (1972)
	1971-1972	123	0.105				Kawai <i>et al.</i> (1973)
	1971-1972		0.038-0.075				Kamata (1973)
	1970		3.780 ^b				Suzuki <i>et al.</i> (1973)
	1971		3.592 ^b				Suzuki <i>et al.</i> (1973)
	1972		3.822 ^b				Suzuki <i>et al.</i> (1973)
	1973		0.0854				Kamata (1974)
	1971-1975		0.172	0.385	0.006		Matsunaga <i>et al.</i> (1975)
		26	0.061	0.067			Anonymous (1975)
	1971-1972	398	0.0626	0.1009	0.0034		Hayashi (1973, 1974)
		10	0.981		0.0051		Inuyama and Takashita (1973)
		10		0.071			Shimamoto <i>et al.</i> (1973)
	1973	7	0.071	0.109	0.002		Sugaya <i>et al.</i> (1976)
	1974		2.436 ^b	2.313 ^b			Suzuki <i>et al.</i> (1976)
			2.353 ^b	2.442 ^b	0.254 ^b		Yamada and Sakamoto (1973)
		10	0.234	0.040	not found	not found	Yakushiji <i>et al.</i> (1979)
	1977	20	1.89 ^b		0.052 ^b		
Turkey							Karakaya <i>et al.</i> (1987)
(Ankara)	1984-1985	61	3.66 ^b	0.97 ^b			Karakaya <i>et al.</i> (1987)
(Adana-Cujurova)	1984-1985	52	10.57 ^b	1.45 ^b			
Oceania							Newton and Greene (1972)
Australia	1970	67	0.014 ^e				Newton and Greene (1972)
	1970	67	0.007 ^f				Newton and Greene (1972)
	1970	67	0.066 ^g				Miller and Fox (1973)
(Brisbane)	1971-1972	20	0.288				Miller and Fox (1973)
(Mareeba)	1971-1972	20	0.415				Siyali (1972)
		45	0.064				Stacy and Thomas (1975)
		22	0.076				Conway <i>et al.</i> (1985)
		14	0.042	0.001	0.013	0.004	Stacey <i>et al.</i> (1985)
(urban)	1979-1980	45	0.046		0.009		Stacey <i>et al.</i> (1985)
(rural)	1979-1980	95	0.041		0.008		Hornabrook <i>et al.</i> (1972)
New Guinea	1972	16	0.004				Hornabrook <i>et al.</i> (1972)
	1972	19	0.015				

^a Maximal value.^b Concentration in milk fat (ppm milk fat).^c Not all samples tested for all compounds.^d Range of values for milk containing 4% fat containing 3.3-6.6 ppm.^e At beginning of feeding, 1.8% fat.^f At middle of feeding, 1.2% fat.^g At end of feeding, 5.1% fat.

Table 15.15
Urinary Excretion of DDA by People in the United States with Varying Degrees of Exposure to DDT^a

Exposure	Year	Number of samples	DDA excretion (ppm)		Reference
			Range	Mean	
General population	1954	8	<0.05	—	Hayes <i>et al.</i> (1956)
	1957	8	<0.02–0.07	—	Hayes <i>et al.</i> (1971)
	1962	23	<0.02–0.18	—	Durham <i>et al.</i> (1965)
	1968	11	0.008–0.019	0.014	Cranmer <i>et al.</i> (1969)
Environmental ^b	1962	13	0.02–0.11	—	Durham <i>et al.</i> (1965)
Applicators	1962	11	0.02–0.17	—	Durham <i>et al.</i> (1965)
Formulators	1957	40	0.12–7.56	1.71	Ortelee (1958)
Makers and Formulators	1966	35	<0.01–2.67	0.97	Laws <i>et al.</i> (1967)
Volunteers given 3.5 mg/day orally	1953–1954	2	0.10–0.42 ^c	0.21 ^b	Hayes <i>et al.</i> (1956)
Volunteers given 35 mg/day orally	1957–1958	6	0.06–1.98 ^d	0.23 ^c	Hayes <i>et al.</i> (1971)
	1953–1954	6	0.69–9.67 ^c	2.46 ^b	Hayes <i>et al.</i> (1956)
	1957–1958	6	0.18–9.21 ^d	3.09 ^c	Hayes <i>et al.</i> (1971)

^a Slightly modified from Hayes (1966) by permission of the National Academy of Sciences.

^b Residents living within 500 ft of agricultural application.

^c Based on all samples after week 35 of dosage.

^d Based on all samples from week 35 through week 93 after dosage started.

indicate a concentration of 0.0358 ppm of DDT-related material expressed as DDT. Although the DDT intakes of these particular groups were not measured, the urinary excretion is of such an order of magnitude that it may account for the excretion of all the absorbed DDT. The excretion of DDA by people with different kinds and degrees of exposure is presented in Table 15.15.

DDT and DDE are excreted in the bile; the concentrations for five men without special exposure varied as follows: *p,p'*- and *o,p'*-DDT combined, 0.0000–0.0009 ppm and *p,p'*-DDE, 0.0005–0.0056 ppm. Higher levels were found in the bile of one pest-control operator (Paschal *et al.*, 1974).

Other Laboratory Findings In the absence of occupational DDT poisoning, there has been no opportunity to explore (as has been done with the cyclodiene insecticides) the relationship between clinical and EEG findings. In fact, the only DDT workers studied in this regard were exposed also to BHC and benzilan, so the findings might have been related to one or more of the compounds or to their interaction. Electroencephalograms were obtained from 73 of these workers exposed for periods ranging from 7 months to 20 years. Just over 78% of the records were normal and 21.9% were abnormal. The most severe changes involved persons exposed to the three compounds for 1–2 years; less severe changes were seen with either shorter or longer exposure. The changes were not correlated with age; the range and mean of age for those judged abnormal were almost identical with these values for persons considered normal. Some of the records showed bitemporal sharp waves with shifting lateralization combined with low-voltage theta activity. Other records showed spike complexes, paroxysmal discharges composed of slow and sharp waves

most pronounced anteriorly, and low-voltage rhythmic spikes posteriorly. None of the persons examined showed any abnormal clinical neurological finding (Israeli and Mayersdorf, 1973; Mayersdorf and Israeli, 1974). The incidence of abnormal electroencephalograms in the general population is 9.0 or 9.2%, according to other investigators cited by Israeli and Mayersdorf. Czegledi-Janko and Avar (1970) considered that nonspecific EEG abnormalities occur in 10–20% of the general population. Under the circumstances, there is some question of whether the results are meaningful.

Clinical laboratory findings associated with DDT poisoning are not diagnostic.

Treatment of Poisoning No useful guidance regarding treatment has been gleaned from the very few cases of DDT poisoning that have occurred. Animal studies indicate that sedatives, ionic calcium, and glucose or another ready source of energy would be useful. On the basis of experience in treating people poisoned by different convulsive poisons, it seems likely that diazepam would be beneficial (see Section 15.2.5).

15.3.2 TDE

15.3.2.1 Identity, Properties, and Uses

Chemical Name TDE is 1,1-dichloro-2,2-bis(4-chlorophenyl)ethane.

Structure See Table 15.2.

Synonyms The common name TDE (ISO) is an acronym for tetrachlorodiphenylethane. Except in France, it is a generally

recognized name for the compound as a synthetic insecticide. This is true even though TDE is an alternative name for an unrelated compound, etoglucid, which is a chemically unrelated antineoplastic drug. For reasons that are obscure, the word DDD (an acronym for *dichlorodiphenyldichloroethane*) is used very much more commonly for 1,1-dichloro-2,2-bis(chlorophenyl)ethane when viewed as a metabolite of DDT or when used as a therapeutic drug, and this distinction has been retained in this book. As it happens, the term DDD also has two meanings; it is used for 2,2'-dihydroxy-6,6'-dinaphthyl disulfide as well as for the compound under discussion. Actually, almost everything we know about the compound relevant to humans is associated with its use as a drug rather than its use as an insecticide. Nonproprietary names for the *o,p'* isomer which is used as a drug include chlodithane (USSR) and mitotane (United States).

A proprietary name for the insecticide is Rhothane®. Code designations include D-3, ENT-4,225, ME-1,700, and NSC-38,721 (for *o,p'* isomer only).

Physical and Chemical Properties TDE has the empirical formula $C_{14}H_{10}Cl_4$ and a molecular weight of 320.05. The pure material forms colorless crystals melting at 109–110°C. The technical material consists mainly of the *p,p'* isomer but also contains a substantial proportion of *o,p'* isomer and lesser proportions of related compounds. *p,p'*-TDE is more slowly dehydrochlorinated than *p,p'*-DDT, but TDE is incompatible with alkali. The solubilities are similar to those of DDT. The density of the technical material is 1.385.

History, Formulations, Uses, and Production The insecticidal properties of TDE were first described by Läuger *et al.* (1944). The formulations have included the technical material; wettable powders, 5%; emulsion concentrates, 25%; and dust, 5 and 10%.

15.3.2.2 Toxicity to Laboratory Animals

Basic Findings The effects of TDE are similar to those of DDT, but TDE is much less toxic in the rat and in humans. Gaines (1969) found the oral LD 50 in both male and female rats to be greater than 4000 mg/kg; Lehman (1951, 1952) reported 3400 mg/kg as an oral LD 50 in rats and 1200 as a dermal value in rabbits. Rabbits were killed quickly by dermal applications at the rate of 400 mg/kg/day; they were made severely ill but did not die when treated at the rate of 200 mg/kg/day for 90 days. In rats fed for 2 years, the lowest dietary level producing gross effects was 400 ppm and the lowest level fed (100 ppm, about 5 mg/kg/day) produced tissue damage. In the rat, pathology is indistinguishable from that caused by DDT (Lehman, 1951, 1952).

Absorption, Distribution, Metabolism, and Excretion The metabolism of *p,p'*-DDD has been described in Section 15.3.1.2.

Regardless of dosage form, 75% or more of *o,p'*-DDD is

absorbed from the gastrointestinal tract (Korpachev, 1972a). Following repeated doses, storage of *o,p'*-DDD reached its highest point in 10–20 days and then decreased somewhat in spite of continued intake. Elimination was rapid after treatment stopped but was detectable longest in the adrenals and adipose tissues (Korpachev, 1972b). The metabolism of *o,p'*-DDD in the rat has been investigated thoroughly by Reif and Sinsheimer (1975); their major results are summarized in Figure 15.3, which also records the metabolites found in humans by Reif *et al.* (1974). More recent studies to explain the covalent binding of *o,p'*-DDD in lung and adrenals are also described in Section 15.3.1.2.

Biochemical Effects The biochemical basis for the action of *o,p'*-DDD on the adrenal is not understood fully in connection with any species. It is clear that marked species differences exist. The mechanism that leads to prompt atrophy in the dog may be quite different from the mechanisms that limit the production or increase the breakdown of corticosteroids in species in which most or all of the adrenal cells stay alive.

It is clear that a reduction of steroid production accompanies atrophy of the adrenal of the dog. A review by Kupfer (1967) considered (a) reduced steroid production in species other than the dog, including the possibility that such reduction is secondary to inhibition of glucose-6-phosphate dehydrogenase activity in the adrenals, and (b) blockage of steroid action by a steroid metabolite formed under the influence of DDD. However, the existence of these effects, much less their importance, remains obscure. Hart and Straw (1971a) showed that administration of *o,p'*-DDD to dogs for only 2–48 hr completely blocked the normal increase in steroid production in response to ACTH *in vitro* but, paradoxically, produced a marked increase in the incorporation of labeled amino acids into protein of the slices. The same authors presented evidence that the site of action is the intramitochondrial conversion of cholesterol to pregnenolone (Hart and Straw, 1971b), specifically, ACTH-activated conversion and not baseline steroid production (Hart and Straw, 1971d). A secondary site involves inhibition of intramitochondrial conversion of 11-deoxycortisol to cortisol (Hart and Straw, 1971d). Further evidence supporting the importance of the primary site was offered by Komissarenko *et al.* (1972). *o,p'*-DDD inhibited ACTH-induced steroid production by more than 97% within 2 hr, and the active principle is either *o,p'*-DDD *per se* or a derivative formed in the adrenal gland of the intact dog (Hart and Straw, 1971c). *o,p'*-DDD applied to liver slices *in vitro* is not effective in reducing ACTH-induced steroidogenesis in the slices. However, the compound did reduce the formation of corticosteroid from progesterone or deoxycorticosterone added to homogenates made from adrenal cortices from dogs, chickens, rats, and human fetuses. These results are consistent with the view that the action of *o,p'*-DDD is to block 11-β-hydroxylation (Kravchenko, 1973). Furthermore, a concentration of 16 ppm produced this effect in a monolayer culture of human fetal adrenal cells (Komissarenko *et al.*, 1971). Martz and Straw (1973) interpreted the decrease in adrenocortical heme and P-450 pro-

duced by *o,p'*-DDD in the dog as a suggestion that the compound is metabolized to a more active form, and this is supported by more recent *in vitro* studies with isolated adrenal mitochondria (Martz and Straw, 1980; Pohland and Counsell, 1985).

There is evidence for a peripheral action of *o,p'*-DDD on steroid transformation in humans also, although the site of action is different. This evidence was obtained by studying the excretion of metabolites of small injected doses of radioactive steroid both before and during administration of the drug. It was concluded that 3β -hydroxy- Δ^5 -steroid dehydrogenase was inhibited (Bradlow *et al.*, 1963).

Further evidence that *o,p'*-DDD has some inhibitory effect on the synthesis of corticosteroids in humans was provided by *in vitro* tests on adrenal tissue removed surgically from patients, some of whom had been under treatment with the drug. Total doses prior to surgery had varied from 324 to 2280 gm and had been given over periods of 1–12 months. Compounds whose synthesis (from radioactive precursors added to incubation flasks) was inhibited in tissue from treated patients were cortisol, corticosterone, 18-hydroxycorticosterone, and aldosterone (Touitou *et al.*, 1978). Direct addition of *o,p'*-DDD to human adrenal tissue *in vitro* was without effect on synthesis of corticosteroids.

Following massive dosage (60 mg/kg, iv), all of the isomers of DDD inhibit ACTH-induced steroid production in the dog, but the inhibition reached 50% of control in only 27 min after dosing with the *m,p'* isomer compared to 87 min with the *o,p'* isomer and 4–18 hr with the *p,p'* isomer. There was a marked temporal correlation between the percentage inhibition of ACTH-induced steroid production, the disruption of normal cellular structure of the innermost zones of the adrenal cortex, and the severity of the damage to mitochondria in these zones caused by the three isomers (Hart *et al.*, 1973). The effectiveness of *m,p'*-DDT for treating metastatic adrenocortical carcinoma had already been demonstrated (Nichols *et al.*, 1961).

However, in humans *m,p'*-DDD is less effective than *o,p'*-DDD (de Fossey *et al.*, 1968), and Reznikov (1973) found *m,p'*-DDD less effective in dogs also. Administration of *o,p'*-DDD to dogs is followed by a decrease in plasma albumin and an increase in globulins, especially α_2 -, β_1 -, and γ -globulins (Vanyurykhina, 1972). The relation of these changes to the suppression of adrenal function is unknown, and their clinical significance is also unknown.

Guinea pigs receiving *o,p'*-DDD intraperitoneally at a rate of 100, 200, or 300 mg/kg/day for 20 days showed decreases in ascorbic acid levels corresponding to dosage (Petrun' and Nikulina, 1970). It was speculated that this might interfere with synthesis of corticosteroids.

Like other chlorinated hydrocarbon insecticides, *o,p'*-DDD stimulates hepatic microsomal oxygenation of both drugs and steroids and, according to a thorough review by Kupfer (1967), this may explain much of its action on corticoid metabolism in a wide range of species. Increased breakdown is evidenced by increased excretion of polar metabolites while nonpolar metabolites remain stable or even decrease—a finding encountered

in human patients (Hellman *et al.*, 1973). However, the demonstrated effect on corticoid metabolism fails to explain why *o,p'*- and *m,p'*-DDD are unique in their overall effects on the adrenal, including their ability to produce adrenocortical atrophy in the dog. Other powerful inducers of microsomal enzymes lack these effects. Furthermore, in some systems DDD is a relatively weak inducer compared, for example, to DDT and DDE (Gillett *et al.*, 1966). Whereas induction does occur in dogs, its interpretation is complex; for example, the induction caused by repeated doses can be suppressed by cortisol (Martz and Straw, 1972). Mikosha (1985) has proposed that inhibition of NADP reduction by malic enzyme in adrenals may play a role in *o,p'*-DDD action, perhaps by causing a decrease in steroid metabolism (Ojima *et al.*, 1985).

Effects on Organs and Tissues DDD is used to control different forms of adrenal overproduction of corticoids in humans (see Section 15.3.2.3). This therapy originally was based on the demonstration that DDD (Nelson and Woodard, 1948, 1949) and especially *o,p'*-DDD (Cueto and Brown, 1958; Komissarenko *et al.*, 1968) cause gross atrophy of the adrenals and degeneration of the cells of its inner cortex in dogs. This is true even though it was reported at the very first (Nelson and Woodard, 1948, 1949) that DDD produces almost no detectable damage to the adrenals of rats, mice, rabbits, and monkeys, and this finding was confirmed and extended by other investigators to other species, including humans (Zimmerman *et al.*, 1956; Komissarenko *et al.*, 1970). In the dog, *o,p'*-DDT produces gross atrophy of the adrenals when administered at a dosage of only 4 mg/kg/day. The dosage of technical grade DDD required to produce the same effect is 50–200 mg/kg/day (Cueto and Brown, 1958). However, in spite of its exceptional susceptibility, there is a definite threshold below which the dog does not respond. About 15% of technical DDT is *o,p'* isomer, much of which is gradually metabolized to *o,p'*-DDD. Yet dogs remained healthy and reproduced normally in a three-generation study involving dosages of technical DDT as high as 10 mg/kg/day (see Section 15.3.1.2).

DDD has been little used for Cushing's syndrome in dogs (Lubberink *et al.*, 1971), but it is effective at lower dosages than those used in humans, and side effects are less serious and less frequent (Schechter *et al.*, 1973).

It is an interesting fact that *p,p'*-DDE and the —OH analog of *p,p'*-DDD causes moderate hypertrophy of the dog adrenal and 2,2-bis(*p*-chorophenyl)ethane causes moderate hyperplasia (Larson *et al.*, 1955).

The adrenal gland of the chicken, like that of the dog, undergoes some degeneration following treatment with *o,p'*-DDD (Komissarenko *et al.*, 1971).

The effect of DDD on thymolymphatic tissues is poorly understood. In one of the earliest studies of the compound, Lillie *et al.* (1947) reported that the spleen of all treated animals showed impressive siderosis. Much later Gawahary (1972) reported that, in rabbits, intramuscular injection of a commercial grade DDD (mainly *p,p'* isomer) caused acute atrophy of the thymus and hypertrophy of the adrenal, although the *m,p'*

isomer at a dosage of 100 mg/kg/day caused *hypertrophy* of the thymus and an increase in its choline acetylase activity. Decrease in the weight of the thymus and spleen as well as the adrenal glands of rats treated with *o,p'*-DDD was reported by Hamid *et al.* (1974).

Furthermore, Cueto and Moran (1968) and Cueto (1970) showed that, at a dosage of 50 mg/kg/day for 14 days, *o,p'*-DDD caused a gradually progressive hypotensive failure in dogs injected with epinephrine or norepinephrine, while leaving unchanged the cardioaccelerator and immediate pressor response of these drugs. The hypotensive failure was associated with weakening of the contractile force of the heart and with a reduction of plasma volume. The latter may have been caused by loss of fluid from the intravascular compartment and was not caused by release of histamine. The hypotensive state could be prevented to a significant degree by pretreatment with prednisolone.

The question of the hepatocarcinogenicity of chlorinated hydrocarbon insecticides is discussed in Section 15.2.3.2. In one test, no conclusion could be reached regarding either *p,p'*- or *o,p'*-DDD (Innes *et al.*, 1969). In another test in mice, *p,p'*-TDE at a dietary level of 250 ppm moderately increased the incidence of liver tumors in males only and increased the incidence of lung tumors in both sexes (Tomatis *et al.*, 1974a). The *o,p'* isomer was protective in rats treated earlier with the established carcinogen dimethylbenz[a]anthracene (DMBA) (Kravt'sova *et al.*, 1971). Leydig cell tumors were reported in the testis of rats receiving *o,p'*-DDD at the rate of 0.6 mg/kg/day for 285–348 days (Lacassagne, 1971). This report is inconsistent with other studies (Lehman, 1951, 1952), and this may indicate that a contaminant was involved. In an NCI study (1978a) there was a possible effect of TDE in causing an increased incidence of follicular cell carcinoma or follicular cell adenoma of the thyroid in male Osborne-Mendel rats but no effects in female B6C3F1 mice.

TDE was found not to be mutagenic in *Drosophila* (Vogel, 1972). It was found mutagenic in two of three indicator organisms in host-mediated tests but not in direct tests, suggesting that a metabolite was the active agent. However, in the same series of studies, both DDT and DDA were negative (Buselmaier *et al.*, 1973).

Pathology In addition to atrophy of the zona fasciculata and zona reticularis in the dog, *o,p'*-DDD changes the ultrastructure of most cell types of the anterior pituitary of that species. The most striking feature is an increase in corticotrophocytes such as is seen following adrenalectomy, and the increase in cells is presumably associated with increased production of ACTH. The hypothalamus also is involved (Gordienko and Kozyritskii, 1970; Gordienko *et al.*, 1973). In spite of their severe nature, the changes produced in the dog adrenal are at least partially reversible (Komissarenko *et al.*, 1972). Dosage-response relationships of mitochondrial swelling and of some other details of pathology in the dog adrenal have been explored by Gordienko and Kozyritskii (1973) and by Powers *et al.* (1974), who also investigated regeneration of the gland.

Hypertrophy of the thyroid in dogs receiving 25 mg/kg and its inhibition in those receiving 50 mg/kg had been reported (Gordienko *et al.*, 1972).

15.3.2.3 Toxicity to Humans

Therapeutic Use Following the demonstration that DDD caused atrophy of a part of the adrenal cortex of dogs, the compound has been used in humans in the hope of controlling excessive cortical secretion or of reducing the size of adrenal tumors. The underlying condition may be hyperplasia or adrenocortical carcinoma. Early attempts using mixed isomers and/or dosages less than 100 mg/kg/day often were ineffective, although side effects might be produced (Sheehan *et al.*, 1953). The dosage of *o,p'*-DDD has varied from 7 to 285 mg/kg/day, but a dosage of approximately 40 or more often 100 mg/kg/day for many weeks has been necessary to produce any benefit in humans (Bergenstal *et al.*, 1960; Gallagher *et al.*, 1962; Bledsoe *et al.*, 1964; Southern *et al.*, 1966a,b; Verdon *et al.*, 1962; Wallace *et al.*, 1961; Komissarenko and Reznikov, 1970; Gutierrez and Crooke, 1980).

The effects of idiopathic hyperplasia may be controlled; in fact, a state of adrenal insufficiency may be produced (Canlorbe *et al.*, 1971; Sizonenko *et al.*, 1974).

o,p'-DDD also may give symptomatic relief of excessive production of androgens from a virilizing adrenal carcinoma (Saez *et al.*, 1971; Helson *et al.*, 1971; Korth-Schutz *et al.*, 1977) or of adrenocortical activity secondary to a tumor that produces ACTH (Carey *et al.*, 1973).

Very early attempts to use DDD for treating Cushing's syndrome often failed because the *o,p'* isomer was not used and sometimes because the dosage was small. This was true of what apparently was the first therapeutic use (Sheehan *et al.*, 1953). Using the *o,p'* isomer, a favorable response is produced in about one-fourth to one-half of patients with inoperable adrenocortical carcinoma (Hutter and Kayhoe, 1966; Canlorbe *et al.*, 1971; Hoffman and Mattox, 1972; Lubitz *et al.*, 1973; Montgomery and Struck, 1973; Gutierrez and Crooke, 1980). In fact, an occasional cure, involving complete regression of metastases, is produced by chemotherapy including *o,p'*-DDD (Schick, 1973; Perevodchikova *et al.*, 1972; Harrison *et al.*, 1973; Pellerin *et al.*, 1975; Rappaport *et al.*, 1978). Other patients may live several years (Bricaire and Luton, 1977; McKierman *et al.*, 1978). More commonly, symptoms are relieved and life is prolonged only about 7–8 months or a little longer (Hutter and Kayhoe, 1966; Canlorbe *et al.*, 1971; Hoffman and Mattox, 1972; Lubitz *et al.*, 1973) or even less (Hajjar *et al.*, 1975). The success of treatment often is indicated early by a reduction of steroid excretion (Hoffman and Mattox, 1972; Lubitz *et al.*, 1973), but steroid excretion may increase, decrease, or remain unchanged (Fukushima *et al.*, 1971). Removal of the tumor and *o,p'*-DDD treatment may be combined (Levy *et al.*, 1985). The success of treatment is greater in Cushing's syndrome due to adrenal hyperplasia (Weisenfeld and Goldner, 1962). An early example of what appeared to be complete cure was reported by Bar-Hay *et al.*

(1964). Ten of 17 patients with this condition experienced cure or remission for 12–32 months after the drug had been withdrawn (Luton *et al.*, 1973).

The large dosage of *o,p'*-DDD necessary to produce clinical benefit often produces general lassitude, anorexia, nausea, vomiting, diarrhea, and/or dermatitis (Southern *et al.*, 1961; Weisenfeld and Goldner, 1962; Danowski *et al.*, 1964; Hutter and Kayhoe, 1966; Bochner *et al.*, 1969; Naruse *et al.*, 1970; Halmi and Lascari, 1971; Hoffman and Mattox, 1972; Nitschke and Link, 1972; Lubitz *et al.*, 1973; Perevodchikova *et al.*, 1972; Hajjar *et al.*, 1975; Gutierrez and Crooke, 1980). Apathy may range from mild dulling of interest to profound psychotic depression (Hoffman and Mattox, 1972). Gynecomastia, hematuria, leukopenia, and thrombocytopenia have been reported more rarely (Luton *et al.*, 1972; Perevodchikova *et al.*, 1972). The symptoms disappear soon after administration of the drug is stopped or the dosage is reduced. Furthermore, some patients do not develop toxicity. A 10-year-old girl received 7500 mg/day for a total of 9 kg without discernible side effects (Helson *et al.*, 1971).

Even large, therapeutic doses of *o,p'*-DDD cause no histological alterations of the adrenals in humans (Wallace *et al.*, 1961). However, electron microscopy revealed degenerative changes in the mitochondria of the zona fasciculata of a patient who had received *o,p'*-DDD at the rate of about 3000 mg/day for 1 month (Temple *et al.*, 1969). Dosages in the therapeutic range (specifically those between 110 and 140 mg/kg/day) produced no detectable injury to the liver, kidney, or bone marrow even though the patients exhibited the reversible symptoms listed earlier (Bergenstal *et al.*, 1960).

Kupfer (1967) reviewed the extensive literature indicating that the effect in humans and other species except the dog is caused by stimulation of corticoid metabolism by massive doses of *o,p'*-DDD and not to any direct effect on the adrenal. Southern *et al.* (1966a,b) agreed that the effect was predominantly extra-adrenal in humans when the drug was first given but offered evidence that adrenal secretion of cortisol eventually was reduced. Even though therapeutic doses eventually have a direct effect on the adrenal, doses encountered by workers exposed to technical DDT do not (Clifford and Weil, 1972; Morgan and Roan, 1973).

Somewhat encouraging results were reported in the use of *p,p'*-DDD for treating diabetics with hyaline vascular changes and hyperpolysaccharidemia (Törnblom, 1959). Apparently, there has been no attempt to use *o,p'*-DDD for this condition.

In addition to its rather extensive use for treating Cushing's syndrome, *o,p'*-DDD has been used in a much lower dosage for treating spomenorrhea associated with hypertrichosis. Menstruation was restored in 13 of 15 women with these conditions, and normal pregnancies occurred in five of them during the treatment period. The babies were normal. There was some improvement in hypertrichosis in nine and no improvement in six (Klotz *et al.*, 1971).

At least part of the action of *o,p'*-DDT in controlling excessive androgens involves its action on their metabolism. It was found in a study of three patients with metastatic adrenal car-

cinoma and one with pernicious anemia that the compound decreased the conversion of labeled androgens to androsterone by about 76% and to etiocholanolone by about 80%. The main effect on androgen metabolism was consistent with induction of microsomal oxidase activity by the drug (Hellmann *et al.*, 1973).

When uptake of radioactive iodine is used for diagnosis of Cushing's syndrome, [¹³¹I]19-iodocholesterol is the compound usually employed. DDD labeled with ¹³¹I has been used for the same purpose (Skromme-Kadlubik *et al.*, 1972, 1973a,b, 1974). No comparative study of the duration of storage of the two compounds appears to have been made. However, it is clear that it is possible to introduce enough radiation via ¹³¹I-labeled DDD either to kill rodents or to cause atrophy of their adrenal glands, depending on the schedule of administration (Skromme-Kadlubik *et al.*, 1974). This has been viewed as an indication that ¹³¹I-labeled DDD might be useful for treating human adrenal carcinoma. It certainly is an indication for caution in using the diagnostic technique in patients not already proved to have adrenal cancer.

Laboratory Findings Analytical study associated with what apparently was the first attempt to use *p,p'*-DDD in treating Cushing's syndrome established that the compound is concentrated in the adrenal gland. Eleven weeks after the last course of DDD, when the concentration in adipose tissue was less than half what it had been earlier, the concentration in an adrenal biopsy was 50 ppm, wet weight. On a lipid basis, the concentrations in fat and adrenal were almost identical (Sheehan *et al.*, 1953). A patient who had received *o,p'*-DDD at the rate of 4000 mg/day for 58 days had a blood level of 6 ppm and excreted 8.3 mg of free and 39.7 mg of conjugated DDA in a 24-hr urine sample (Sinsheimer *et al.*, 1972). There is evidence for two plasma pools of *o,p'*-DDD (Slooten *et al.*, 1982).

Normal volunteers excreted increased concentrations of DDA within 24 hr of receiving *p,p'*-DDD at a rate of 5 mg/day and continued to excrete DDA at greater than predose levels for over 4 months after dosing was stopped after 81 days (Roan *et al.*, 1971).

Treatment of appropriate cases with *o,p'*-DDT usually results in a decrease in urinary steroid excretion (Gutierrez and Crooke, 1980). An unusually detailed study of the individual compounds is that of Hartwig *et al.*, (1968).

In long-term administration of *o,p'*-DDD (2 gm/day for 1–3 months) to patients with adrenal carcinoma or Cushing's syndrome, Ojima *et al.* (1984) found that plasma levels of pregnenolone, progesterone, cortisol, corticosterone, and some other C₂₁ steroids were progressively decreased, as well as urinary excretion of 17-ketosteroids and 17-hydroxycorticosteroids. Touitou *et al.* (1985), however, have been unable to demonstrate any correlation between concentrations of *o,p'*-DDD in adrenals removed from patients preoperatively treated with the drug for Cushing's syndrome and inhibition of some steroid biosynthesis enzymes measured *in vitro*. There is a suggestion that *o,p'*-DDD suppresses ACTH-secreting cells in

[785 through 867 omitted]

decone in the stool; the intestine itself seemed the most likely source (Boylan *et al.*, 1979). These observations also strongly suggest that reabsorption of chlordeneone from the intestine is largely dependent on the presence of bile.

The chlordeneol found in human bile from poisoned workers was not present as the free alcohol to any great extent but mainly existed as the glucuronide (Fariss *et al.*, 1980). Another conjugate of chlordeneone was also detected, possibly formed by conjugation with glutathione. Unlike rat liver, human liver and gerbil liver (see Section 15.7.2.2) formed chlordeneol by the action of an aldo-keto reductase (Molowa *et al.*, 1986a). The enzyme has been purified from human liver (Molowa *et al.*, 1986b). In fact, immunoblot analyses of seven human liver samples showed the presence in four of two immunoreactive proteins whose total concentration varied over a sixfold range. Interestingly, the half-time for the disappearance of chlordeneone from 22 exposed workers also varied as much as sixfold and was independent of the amount of chlordeneone initially detected in the blood (Cohn *et al.*, 1978). Of 28 chlordeneone-poisoned workers, only 8 patients had normal sperm counts and motility and only in one of these was chlordeneone greater than 1 ppm of blood (Cohn *et al.*, 1978; Guzelian, 1981, 1982b). Arrest of sperm maturation was also observed in testicular biopsies of two patients (Guzelian, 1982b).

Pathology Five sural nerve biopsies from workers affected by chlordeneone revealed an accumulation of elongated, electron-dense, crystalloid rods and short, laminated, and parallel-membranous bodies within Schwann cell cytoplasm; redundant Schwann cell cytoplasmic folds; prominent collagen pockets, focal degradation of axon cylinders containing condensed neurofilaments, neurotubules, and dense bodies; occasional demyelinated axons; and vacuolization of nonmyelinated fibers. The predominance of involvement of nonmyelinated and smaller myelinated fibers and relative sparing of the larger myelinated fibers may explain the clinical symptomatology and electromyographic findings (Martinez *et al.*, 1978).

Six skeletal muscle biopsies from the same group of workers revealed accumulations of lipofuscin and amorphous, electron-dense structures below the sarcolemma and between myofibrils of skeletal muscle (Martinez *et al.*, 1978).

Needle liver biopsies from chlordeneone-poisoned men showed minimal steatosis, focal proliferation of reticuloendothelial cells, and hypoglycogenation of nuclei. Livers were enlarged, and electron microscopic examinations showed residual bodies, branched mitochondria with paracrystalline inclusions, and proliferation of the endoplasmic reticulum (Guzelian *et al.*, 1980; Guzelian, 1985). Workers also had high levels of urinary glucaric acid, which is proposed to be derived from the hepatic endoplasmic reticulum. In addition, workers displayed an enhanced clearance of antipyrine from the blood, which usually is taken as a sign of induction of the hepatic cytochrome P-450 drug-metabolizing system.

Discussion Whereas the acute toxicity of chlordeneone is only moderate, its high degree of cumulative effect in mice (Huber, 1965) is remarkable, and it was the subject of early publication.

In fact, the protracted nature of poisoning was known to the original manufacturer before production was first started (see Gleason *et al.*, 1963, reporting brief but critical information supplied by the manufacturer).

A point that deserves more emphasis than it has received is that chlordeneone is stored even more tenaciously by humans than by rodents. There was no way to predict this species difference, but routine analysis of serum samples would have detected the difference when little or no injury had occurred, and the results would have served as a warning to stop exposure. The was one that would be alarming in connection with serum levels of other, more thoroughly studied chlorinated hydrocarbon insecticides. There seems little doubt that poisoning would have been avoided if proper attention had been given to the chemical and clinical aspects of occupational medicine and to the basic considerations of occupational hygiene.

It is interesting how much of the toxicity of chlordeneone in humans can be reproduced in experimental animals, and vice versa, especially if care is taken to pick the right model for a particular effect. This includes enlargement of the liver and induction of the drug-metabolizing system, an important point for toxicological and carcinogenic considerations. Unlike many poisoning episodes, the exposure of workers to chlordeneone has been used to investigate basic toxicological principles in humans with useful results such as the interindividual variability of a previously unknown aldo-keto reductase in liver (Molowa *et al.*, 1986b). Rational treatments for poisonings by these types of chemicals have also emerged (Guzelian, 1982a).

Treatment of Poisoning The only drug that has proved useful in poisoning by chlordeneone is cholestyramine. The use of this agent arose from careful consideration of data on the excretion of chlordeneone by humans and animals, followed by logical experiments in rats and humans (Boylan *et al.*, 1978; Cohn *et al.*, 1978; Guzelian, 1981, 1982a, 1984, 1985). Its effects may be due not only to direct binding of chlordeneone but to binding of bile salts which inhibit the nonbiliary intestinal excretion (Guzelian, 1982b). Because there is reason to think that cholestyramine might be useful for treating poisoning by some other chlorinated hydrocarbon insecticides also, it is described in Section 15.2.5.1. In spite of the importance of cholestyramine in the treatment of poisoning by chlordeneone, other matters relevant to treating poisoning by chlorinated hydrocarbon insecticides ought to be considered (see Section 15.2.5).

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